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NOVEL PHOTOCHEMICAL METHODOLOGIES FOR DIVERSITY ORIENTED
SYNTHESIS AND SCREENING OF COMBINATORIAL LIBRARIES

A Dissertation

Presented to

The Faculty of Natural Sciences and Mathematics

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In Partial Fulfillment

Of the Requirements for the Degree

Doctor of Philosophy

by

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August 2010

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Title: NOVEL PHOTOCHEMICAL METHODOLOGIES FOR DIVERSITY ORIENTED SYNTHESIS AND SCREENING OF COMBINATORIAL LIBRARIES

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Abstract

The main goal of this project was to develop an efficient methodology allowing rapid access to structurally diverse scaffolds decorated with various functional groups.

Initially, we discovered and subsequently developed an experimentally straightforward, high-yielding photoinduced conversion of readily accessible diverse starting materials into polycyclic aldehydes and their (hemi)acetals decorated by various pendants. The two step sequence, involving the *Diels-Alder* addition of heterocyclic chalcones and other benzoyl ethylenes to a variety of dienes, followed by the *Paternò-Büchi* reaction, was described as an alkene-carbonyl oxametathesis. This methodology offers a rapid increase in molecular complexity and diversity of the target scaffolds [30].

To develop this novel methodology further and explore its generality, we directed our attention to the *Diels-Alder* adducts based on various chromones. We discovered that the *Diels-Alder* adducts of chromones are capable of photoinduced alkene-arene [2+2] cycloaddition producing different dienes, which can either dimerize or be introduced into a double-tandem $[4_{\pi}+2_{\pi}]^{\circ}[2_{\pi}+2_{\pi}]^{\circ}[4_{\pi}+2_{\pi}]^{\circ}[2_{\pi}+2_{\pi}]$ synthetic sequence, followed by an acid-catalyzed oxametathesis, leading to a rapid expansion of molecular complexity over a few experimentally simple steps [35].

In view of the fact that oxametathesis previously was primarily observed in aromatic oxetanes, we decided to prepare model aliphatic oxetanes with a conformationally unconstrained or “flexible” methyl group based on the *Diels-Alder*

adducts of cyclohexadiene or cyclopentadiene with methyl vinyl ketone. Upon addition of an acid, the expected oxametathesis occurred with results similar to those observed in the aromatic series [30, 35] proving the generality of this approach. Also we synthesized polycyclic oxetanes resulting from the *Diels-Alder* adducts of cyclic ketones. This not only gave us access to remarkably strained oxetane systems, but also the mechanism for their protolytic ring opening provided a great deal of insight to how the strain affects the reactivity.

Additionally, we discovered that although the model *Hetero-Diels-Alder* adducts did not undergo [2+2] cycloaddition, both *exo*- and *endo-Sulfa-Diels-Alder* products, nonetheless, were photochemically active and various products with defined stereochemistry could be produced upon photolysis.

In conclusion, we have developed an approach to the encoding and screening of solution phase libraries based on the photorelease of externally sensitized photolabile tags. The encoding tags can be released into solution only when a binding event occurs between the ligand and the receptor, equipped with an electron transfer sensitizer. The released tags are analyzed in solution revealing the identity of the lead ligand or narrowing the range of potential leads [50].

Acknowledgements

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Table of Abbreviations and Acronyms

Δ	temperature (heat)
1CR	one-component reaction
2CR	two-component reaction
3CR	three-component reaction
4CR	four-component reaction
5CR	five-component reaction
6CR	six-component reaction
7CR	seven-component reaction
Ac	acetyl
Ach	acetylcholine
aq.	aqueous
Ar	aryl
Bn	benzyl
Bz	benzoyl
<i>n</i> -Bu	<i>normal</i> -butyl
cat.	catalyst (or catalytic amount)
calcd	calculated
COT	1,3,5,7-cyclooctatetraene
Cp	cyclopentadienyl
DAMN	2,3-diaminomaleonitrile
DBB	4,4'-di- <i>tert</i> -butylbiphenyl

DCB	1,4-dicyanobenzene
DCC	Dynamic Combinatorial Chemistry
DCL	Dynamic Combinatorial Library
DCM	dichloromethane
DIC	<i>N,N'</i> -diisopropylcarbodiimide
DIEA (DIPEA)	<i>N,N</i> -diisopropylethylamine (Hünig's base)
DOS	diversity oriented synthesis
DPC	dodecyl phosphocholine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
<i>D.-A.</i>	<i>Diels-Alder</i>
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
eq	equivalent
ERG	electron releasing (donating) group
ESI	electrospray ionization
Et	ethyl
ETS	electron transfer sensitizer
EWG	electron withdrawing group
FDA	Food and Drug Administration
GABA	γ -aminobutyric acid
GCMS	Gas Chromatography-Mass Spectrometry

HBTU	<i>O</i> -benzotriazole-1-yl- <i>N,N,N',N'</i> -tetramethyluronium hexafluoro-phosphate
<i>H.-D.-A.</i>	<i>Hetero-Diels-Alder</i>
HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrum
HOBt	1-hydroxybenzotriazole
h ν	light
IMDA	intramolecular <i>Diels-Alder</i>
IC	internal conversion
ISC	intersystem crossing
LDA	lithium diisopropylamide
MCR	multicomponent reaction
MCPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
NHS	<i>N</i> -hydroxysuccinimide
NMR	Nuclear Magnetic Resonance
ODPM	oxa-di- π -methane
ORTEP	Oak Ridge Thermal Ellipsoid Plot program
[O]	oxidizing reagent
<i>P.-B.</i>	<i>Paternò-Büchi</i>
Ph	phenyl
<i>i</i> -Pr	<i>iso</i> -propyl

Py (py)	pyridine (or pyridyl)
r.t.	room temperature
S ₁	first singlet excited state
sat.	saturated
soln	solution
T ₁ (T ₂)	first (second) triplet excited state
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	tetramethylsilane
<i>p</i> -Ts	<i>para</i> -toluenesulfonyl (4-toluenesulfonyl)
UV	ultraviolet

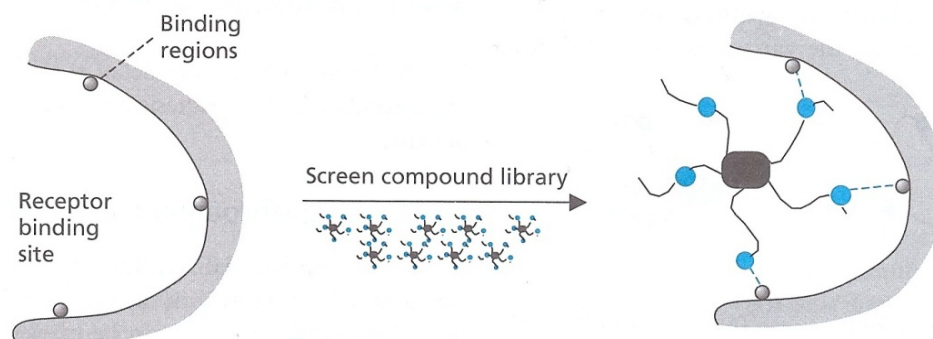
Chapter One: Literature review

A. Drug discovery.

A large portion of research in chemistry these days is driven by big pharma and research institutes, which are trying to find either new biologically active compounds or improve pharmacokinetic and pharmacodynamic properties of recently discovered and well-known drugs. Drug discovery, design and development are long processes which take decades. A **lead compound** – a compound with desired pharmaceutical activity [1] – may be discovered in various ways: (1) screening of natural products; (2) screening of synthetic combinatorial libraries; (3) improving existing drugs; (4) starting from a natural ligand or modulator; (5) combinatorial synthesis; (6) computer-aided design; (7) serendipity, etc.

From a basic knowledge of medicinal chemistry we know what is necessary for a potential lead compound to gain a higher “drug score” or be more “drug-like”. **Lipinski’s** rule of five [1] is a well-known criterion, which is, however, more often violated by new discovered drugs. The approach based on branched or “spider-like” molecules increases the chances of finding a lead compound (Scheme 1). The “arms” contain various functional groups, which are used to probe a binding site for binding regions. The chances of success in finding a lead compound are much greater if the “arms” are evenly spread around the scaffold. Even though a “drug score” can be estimated for any

molecule, it does not evaluate the actual specific effect that the drug exerts (biological activity) [1].



Scheme 1. “Spider-like” molecule probing for an interaction [1].

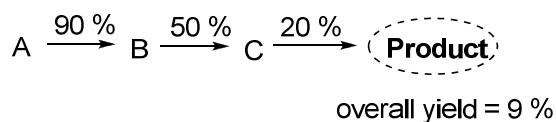
Although many companies are still relying on rational drug design, generally we have a vague idea of what a good drug must look like. The creation and screening of synthetic combinatorial libraries is an elegant method to find a lead compound. Such a library can be prepared through *combinatorial synthesis* – a technology for creating structurally related molecules in large quantity and testing them rapidly for desirable properties – or by using *diversity oriented synthesis* approach – a strategy used to create a massively diverse set of molecules with an emphasis on structural diversity (structurally unrelated compounds).

B. Diversity oriented synthesis.

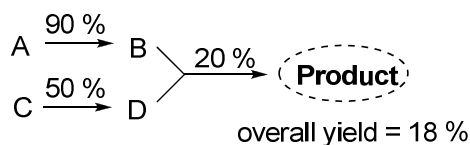
Diversity Oriented Synthesis (DOS) represents the synthesis of moderately small libraries of organic molecules (compared to combinatorial libraries) that have a greater variety of core structures, are structurally more complex, and possess richer stereochemical variations than those produced by traditional combinatorial chemistry [2]. DOS includes two alternative strategies: *convergent* and *divergent* syntheses.

1. Convergent synthesis.

Convergent synthesis is an approach which is designed to improve the efficiency of multi-step chemical synthesis. In a very simple “linear” synthesis the overall yield quickly drops with each reaction step [3a-c]:



Suppose the yields are 90%, 50% and 20% respectively for each consecutive step, then the overall yield of **Product** is only 9% from A. In convergent synthesis the overall yield of **Product** is dramatically improved and now equals 18%:



Convergent synthesis is mostly utilized in the synthesis of complex molecules, biologically active compounds and natural products; it is also known as *total synthesis* – a broad area of modern organic chemistry designed to produce complex, biologically important structures from simple building blocks (starting materials) usually without assistance from biological processes.

1.1 First total synthesis of natural compounds.

The beginning of total synthesis occurred in the nineteenth century. In 1828 Wöhler reported the very first “total” synthesis of *urea* – a natural product [4a]. This event can be considered the beginning of organic synthesis and the first example, where an organic compound was synthesized from inorganic substances. Kolbe’s synthesis of acetic acid is the second major achievement in the history of synthetic organic chemistry.

But the most profound total synthesis at that time was performed by E. Fischer, when he obtained (+)-glucose (Figure 1):

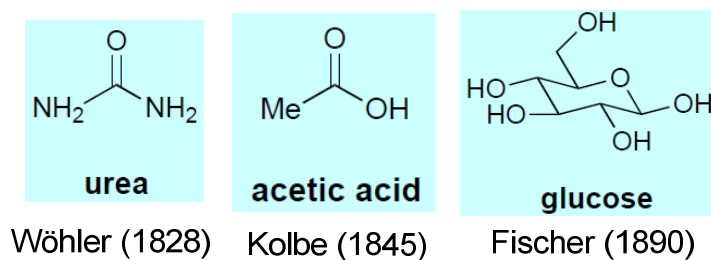


Figure 1. Selected 19th century total syntheses of natural products [4a].

With the help of technological progress and tremendous scientific advancement, the twentieth century changed the entire look on synthetic organic chemistry. Woodward's achievements in total synthesis between 1944 and 1981 were the most prominent at that time. E. J. Corey introduced *retrosynthetic analysis* into organic chemistry – the logic of chemical synthesis, helping to analyze complex target molecules and come up with possible synthetic pathways for their construction [4a]. He received the Nobel Prize in chemistry in 1990, having synthesized hundreds of natural and designed products between 1960 and 1991 (Figure 2):

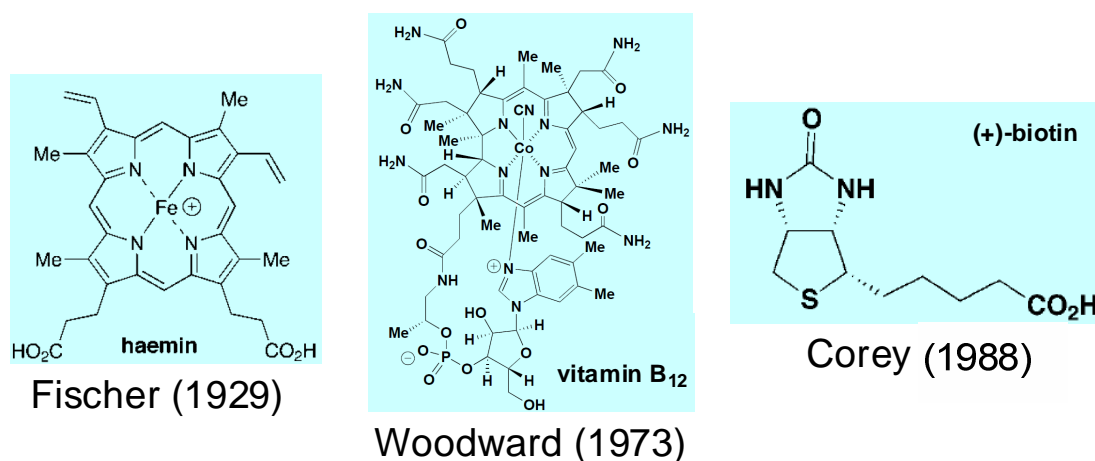


Figure 2. Selected 20th century total syntheses of natural products [4a].

1.2 Examples of modern total syntheses.

The chemical literature of the twentieth century abounds with hundreds of examples of total syntheses of natural products. Every new published structure is even more complicated and challenging than the previous one. Each reported synthetic pathway is more daring and revolutionary than the other. I will focus mostly on methodological breakthroughs relevant to this dissertation because it is absolutely not possible to even select the most important and striking examples. However, it is still worth mentioning a few molecules that have “changed the world”.

Taxol is one of such compounds. It was isolated from the Pacific yew tree, *Taxus brevifolia*. Its structure was reported in 1971 and only twenty years later it was approved by FDA for the treatment of ovarian, breast and lung cancers. It is also used in the treatment of Kaposi's sarcoma. Its first total synthesis was reported in 1994 [4b-c].

Brevetoxin B is another “amazing” molecule. Its architecture includes eleven rings and twenty three stereogenic centers. Brevetoxins are neurotoxins that bind to voltage-gated sodium channels in nerve cells, leading to disruption of normal neurological processes. After several attempts it was finally synthesized in 1995 [4d-e].

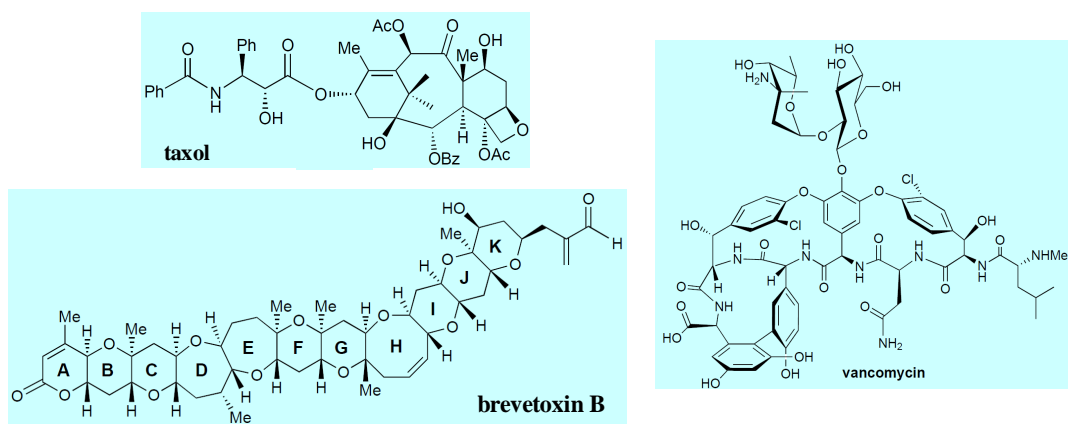


Figure 3. “Molecules that changed the world” [4a].

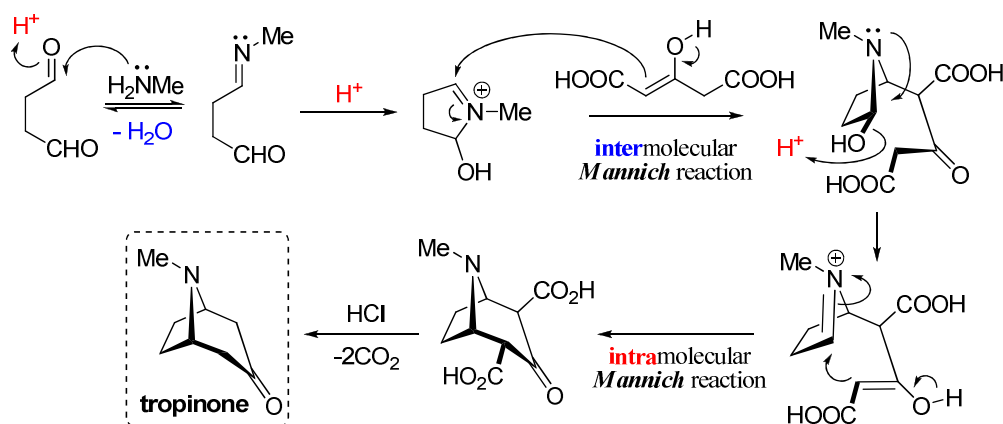
Vancomycin is a glycopeptide antibiotic used in the prophylaxis and treatment of infections caused by Gram-positive bacteria. It was isolated in the 1950s, the structure was revealed in 1982 and the first total synthesis was reported in 1999 (Figure 3) [4a, 4f].

1.3 Cascade reactions.

While more and more exotic chemical structures were required to be synthesized, chemists continued discovering and developing more sophisticated methodologies. A typical total synthesis may include more than thirty steps. If each step is at least 90%, total yield of the synthesis can be as low as $(0.9)^{30} * 100\% = 4\%$. One way to overcome this complication and inefficiency is to develop a method where several transformations are carried out in one reaction vessel in tandem. Such transformations are called **cascade** reactions (or **tandem** or **domino** reactions).

1.3.1 Robinson's synthesis.

Perhaps the first example of a cascade reaction, which was utilized in total synthesis, was a tandem sequence reported in 1917 by Robert Robinson [5]. His biomimetic synthesis, which aimed to obtain tropinone – a natural alkaloid, includes two consecutive Mannich reactions (Scheme 2):

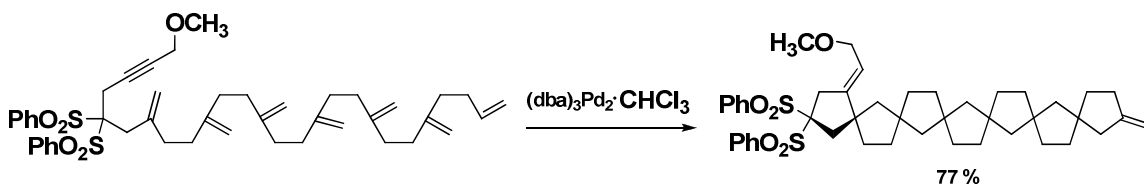


Scheme 2. Total synthesis of tropinone (Robinson, 1917) [5].

The first one is an *inter*-molecular and the second is an *intra*-molecular reaction. Tropinone was eventually obtained in a simple one-pot procedure.

1.3.2 Palladium catalyzed tandem sequences.

Another striking example of a cascade reaction is the cycloisomerization of polyenyne with a catalyst derived from Pd(0), acetic acid and a ligand to polycycles. The process involves the stages of initiation (by addition of Pd-H to an acetylene), propagation (by intramolecular carbopalladation) and termination (by β -hydrogen elimination). Increasing the number of double bonds is directly related to the number of rings formed [6] (Scheme 3):



Scheme 3. A Palladium zipper [6].

This approach for construction of polycycles can be considered equivalent to a palladium zipper, in which the π orbitals are the “teeth” and the palladium complex in the “tab”. Closing the zipper stitches the π bonds into σ bonds with creation of the polycycles.

1.3.3 Ladder Polyether Synthesis.

The ladder polyether natural products (Figure 4) are an amazing family of molecules that have very complex structures, demonstrate exceptionally potent and dramatic biological effects, and are the toxic constituents of marine phenomena known collectively as Red Tide. All of the junctions between the fused rings are *trans*, and consecutive ring junctions are *syn* to one another. This trans-syn combination is

responsible for the “ladder” topography of these molecules. Twenty years ago Nakanishi hypothesized that a polyepoxide may transform into a ladder polyether via a cascade of epoxide-opening events [7].

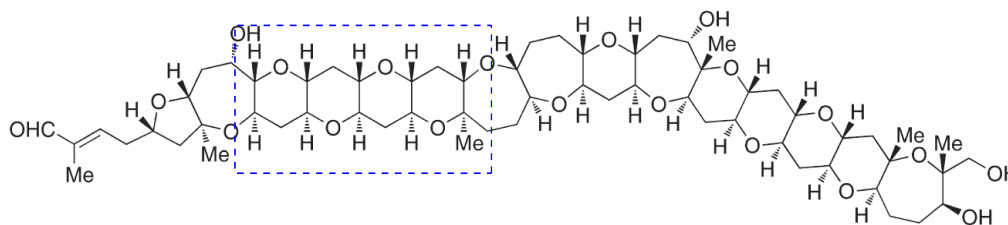
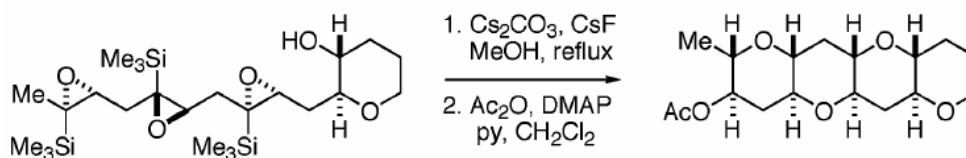


Figure 4. A ladder polyether – **gymnocin B**.

Many attempts to form ladder polyethers have been reported, but in multiple cases *exo* regioselectivity tends to dominate. Recently a method based on removable trimethylsilyl (SiMe_3) was published (Scheme 4). This functional group dictates the regioselectivity of epoxide opening and leaves no trace of itself by the time the cascade has come to an end [7].



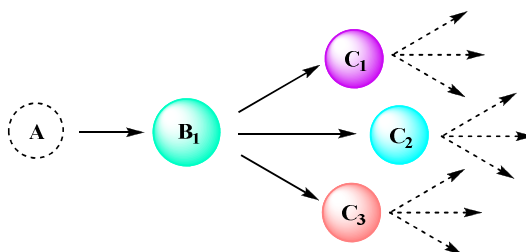
Scheme 4. Cascade cyclization of polyepoxysilanes under basic conditions [7].

A cascade reaction is sometimes called a living reaction because it shares some characteristics with a *living polymerization*.

2. Divergent synthesis.

In chemistry a divergent synthesis is an alternative approach with intent to improve the efficiency of chemical synthesis. It is often an alternative to convergent synthesis [8a-b]. Divergent synthesis aims to generate a library of structurally unrelated

chemical compounds. Each successive generation of compounds is generated by further reactions with each compound in the previous generation. This methodology quickly diverges to large numbers of new compounds (Scheme 5):

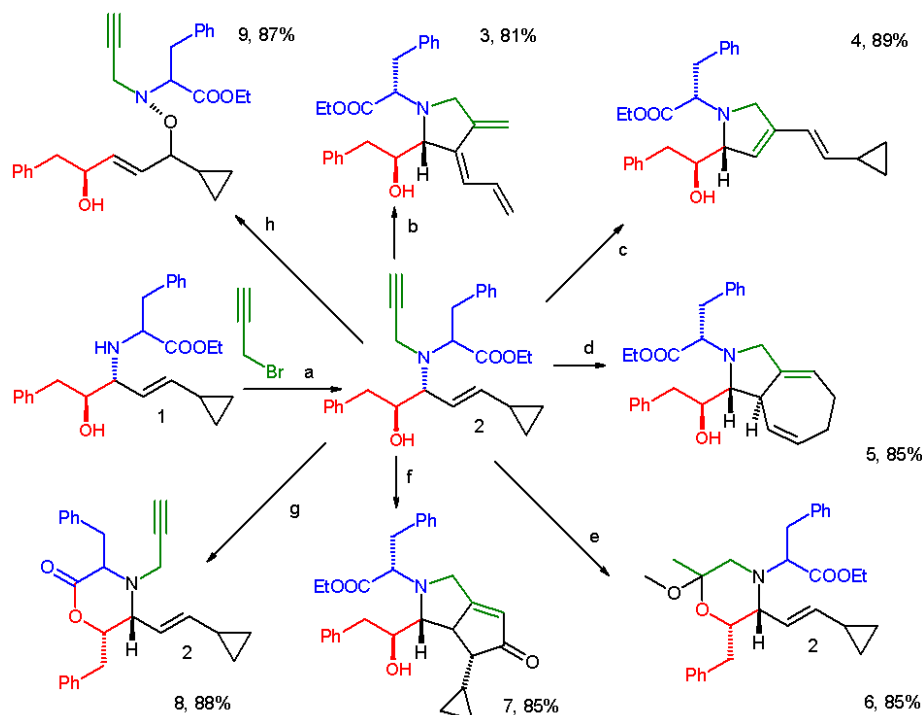


Scheme 5. Divergent synthesis produces a large number of new compounds.

In another strategy, divergent synthesis begins from a molecule as a central core from which consecutive generations of building blocks are added. A good example is the divergent synthesis of dendrimers, where in each generation a new monomer reacts to the growing surface of the sphere [8a-b].

One of the most striking examples of diversity oriented synthesis was reported by Schreiber in 2006 [9]. A short and efficient pathway was found that uses intramolecular cyclization reactions of readily synthesized and functionalized amino alcohols. They used the *Petasis* three-component, boronic acid Mannich reaction followed by an amine propargylation to yield β -amino alcohol (**2.6**) (compound **2**, Scheme 6). Then a series of skeletal diversification reactions with (**2.6**) was explored. Cycloisomerization catalyzed by $[\text{Pd}(\text{PPh}_3)_2(\text{OAc})_2]$ ended up in opening of the cyclopropyl ring to afford triene (**3.6**) by β -hydrogen elimination/reductive elimination sequence. Enyne metathesis of (**2.6**) using *Hoveyda-Grubbs* catalyst gave diene (**4.6**). Cycloisomerization catalyzed by $[\text{CpRu}(\text{MeCN})_3\text{PF}_6]$ resulted in a [5+2] reaction to afford cyclic diene (**5.6**) by a cyclopropyl ring-opening/reductive elimination sequence. Electrophilic activation of the

alkyne in (**2.6**) with NaAuCl₄ in MeOH led to the intramolecular cyclization of the hydroxyl group followed by incorporation of MeOH to give a morpholine skeleton (**6.6**).



Scheme 6. Skeletal diversification of β -amino alcohol (**2.6**).

The *Pauson-Khand* reaction of (**2.6**) with [Co₂(CO)₈] in the presence of trimethylamine *N*-oxide produced azabicyclo[3.3.0] (**7.6**). Treatment of (**2.6**) with NaH at room temperature gave lactone (**8.6**). Finally, reaction of (**2.6**) with MCPBA yielded product (**9.6**) (Scheme 6).

2.1 Multicomponent reactions.

Divergent synthesis is heavily dependent on densely functionalized compounds. Such compounds often require time and money consuming multistep syntheses. A desired product, however, can be also obtained in a one-pot reaction of three or more starting materials – a *multicomponent* reaction (MCR). Even though MCRs are convergent (Figure 5), they lead to complex molecules decorated by a variety of pendants. Such

structures can be further converted in a diversity oriented fashion to produce various products with unique topology [10].

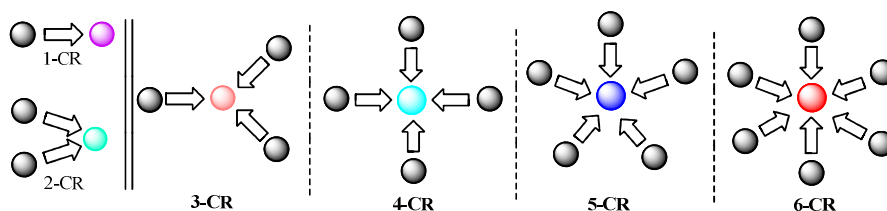
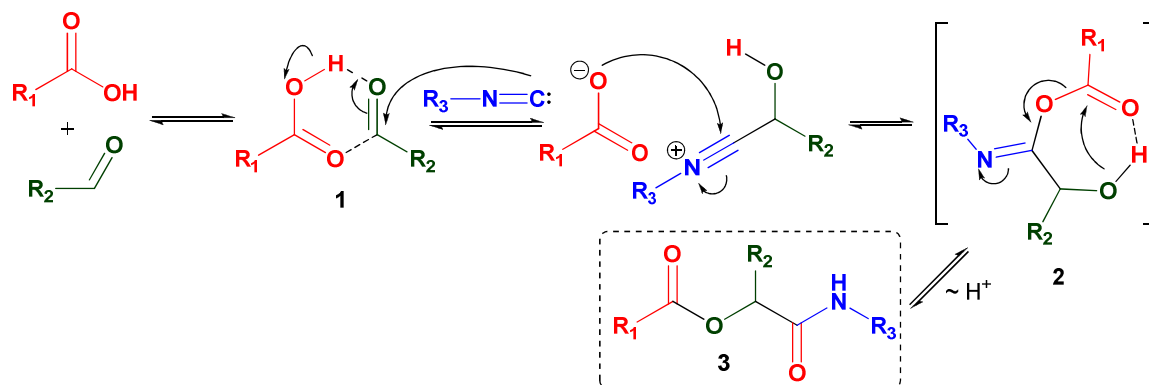


Figure 5. Multi-component reactions.

MCRs have been known for more than 150 years. It should be mentioned that in MCRs the starting materials do not react simultaneously in one step, but rather in a sequence of elementary steps according to a prescribed program. The first three-component reaction was discovered in 1838 by Strecker [10] during his attempt to synthesize α -amino acids via α -amino cyanides. But the most important reaction was described by Mario Passerini in 1921 [10].

2.1.1 Three-component reactions (*Passerini reaction – 3CR*).

The ***Passerini*** reaction involves an isocyanide, a carbonyl and a carboxylic acid to form an α -acyloxy amide (**3.7**) (compound **3**, Scheme 7):



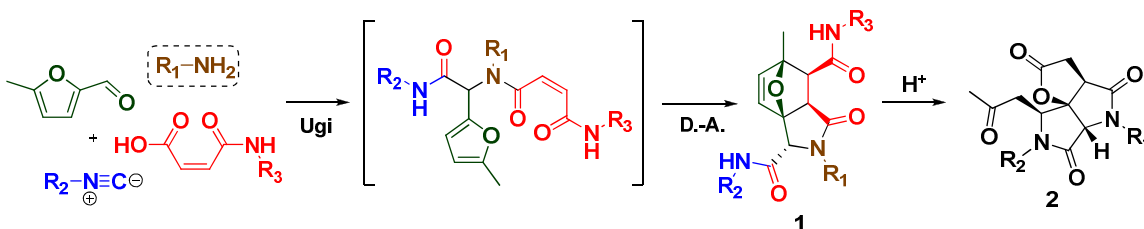
Scheme 7. Suggested mechanism of the Passerini reaction [10].

The mechanism involves the formation of a loosely H-bonded adduct (**1.7**) from a carbonyl and a carboxylic acid, followed by the α -addition of the electrophilic carbonyl carbon and the nucleophilic oxygen atom of the carboxylic acid to the isocyanide carbon leading to the formation of a cyclic transition state with all three compounds. Intermediate (**2.7**), which cannot be isolated, rearranges in an intramolecular transacylation to the stable α -acyloxy carboxamide (**3.7**) [10].

2.1.2 Four-component reactions (*Ugi reaction – 4CR*).

In 1959, Ugi described the most important variants of the four-component condensation, the **Ugi** reaction. Carboxylic acids, hydrazoic acids, cyanates, thiocyanates, carbonic acid monoesters, salts of secondary amines, water, hydrogen sulfide as $\text{Na}_2\text{S}_2\text{O}_3$ and hydrogen selenide as the acid components in the *Ugi* reaction react with ketones or aldehydes, primary and secondary amines, hydrazines and hydroxylamines as the amine components, and C-isocyanides [10].

For instance, an interesting tandem Ugi – Intramolecular *Diels-Alder* (IMDA) reaction was discovered in 2006 [11]. Tricyclic adducts (**1.8**) resulting from the Ugi four-component condensation of a furfural, a monoderivatized maleic acid, a primary amine, and an isonitrile followed by IMDA further rearranged in 85% H_3PO_4 providing (**2.8**) (Scheme 8):



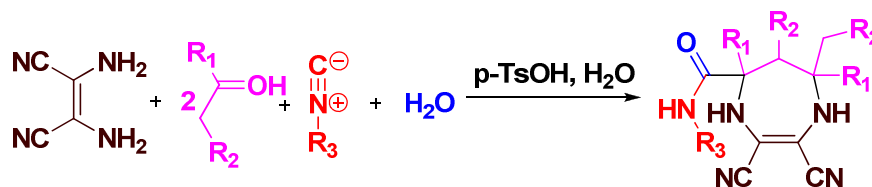
Scheme 8. Ugi/IMDA reaction product and its acid-promoted transformation.

Due to the technical simplicity and high yield, the process can be viewed as a promising chemotype-differential tool in DOS of novel compound libraries for biological screening.

There are not many “original” or named four-component reactions. Another example is the *Asinger* reaction. An α -halogenated carbonyl-component reacts with NaSH and forms *in situ* a thiole. The thiole reacts directly with another carbonyl-component and ammonia to form thiazolines [12].

2.1.3 Five-component reactions (5CR).

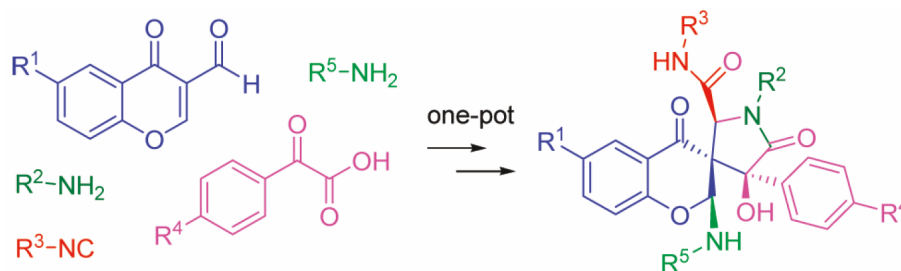
Cases of 5CR are less common. In 2008 Shaabani and co-workers [13] described a one-pot pseudo-five-component synthesis of 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives starting from simple and readily available inputs including 2,3-diaminomaleonitrile (DAMN), ketones, an isocyanide, and water in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 9):



Scheme 9. Pseudo-five-component synthesis of 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives [13].

It is likely that the initial event is the formation of diimine from condensation between DAMN and the ketones. Then an intramolecular imine-enamine cyclization produces a seven-membered ring. After a nucleophilic attack of isocyanide to iminium followed by a nucleophilic attack of a H₂O molecule on the nitrilium moiety and subsequent tautomerization of a new intermediate, the final product is formed.

Another example of a one-pot, two-step, five-component synthesis [14] is based on an Ugi four-component condensation of 3-formylchromones with amines, isocyanides, and glyoxylic acids followed by a nucleophilic Michael addition and intramolecular cyclization. The experimental minimalism and tolerance to a large variety of substituents makes this method utilizable for combinatorial synthesis (Scheme 10):

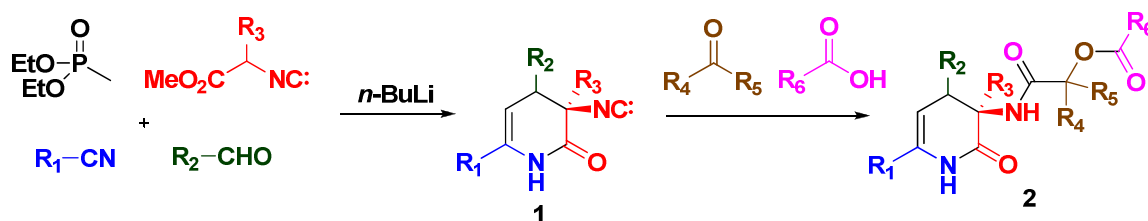


Scheme 10. Five-component synthesis of spiropyrrolidinochromanones [14].

2.1.4 Six-component reactions (6CR).

The exact nature of this sort of reactions is rather complicated to assess; a simultaneous interaction of three or more different molecules is less likely, resulting in a low reaction rate. These reactions are more likely to involve a series of bimolecular reactions.

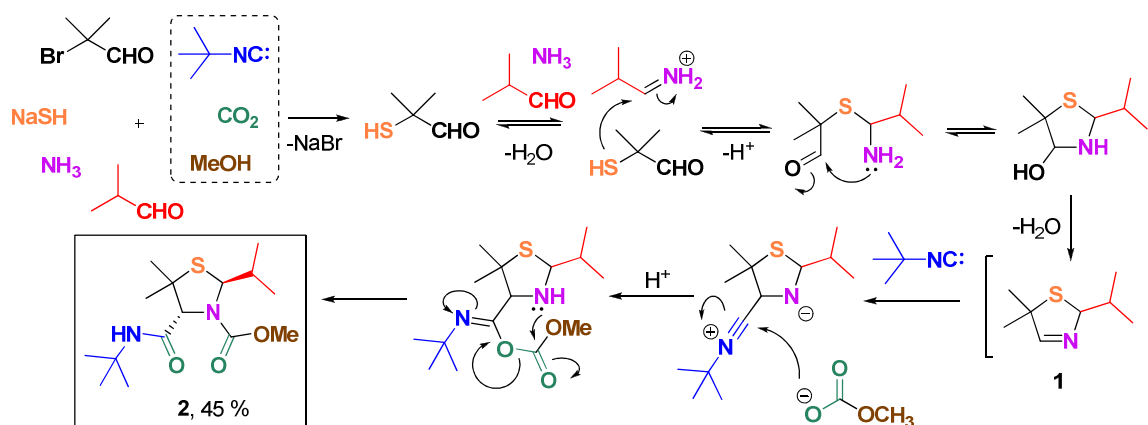
Functionalized depsipeptides (**2.11**) based on a dihydropyridin-2-one core were synthesized by the combination of a 4CR and a 5CR [15]. The synthesis combines a one-pot *Horner-Wadsworth-Emmons* cyclocondensation sequence leading to isonitrile functionalized 3,4-dihydropyridine-2-ones (**1.11**) with an isonitrile-based *Passerini* MCR. The two MCRs could also be performed as a one-pot procedure, simplifying the protocol and leading to a new and highly variable 6CR (Scheme 11):



Scheme 11. MCR leading to depsipeptides [15].

2.1.5 Seven-component reactions (7CR).

Although reports on novel MCRs appear regularly in recent literature, MCRs using more than five components are extremely rare. A milestone in this context is the seven-component reaction (7CR) reported by Dömling and Ugi [10, 16], which was essentially a one-pot combination of a modified *Asinger* and *Ugi* reactions. In this 7CR, two different aldehydes, NaSH, NH₃, an isocyanide, CO₂, and a primary alcohol are combined to produce triazoline (**1.12**) first and then thiazolidine (**2.12**) efficiently. However, NaSH, NH₃, and CO₂ are invariable components in this reaction (Scheme 12):



Scheme 12. Seven-component *Asinger-Ugi* reaction [16].

2.2 Photochemical reactions.

Organic photochemistry is a sub-discipline of organic chemistry concerned with structures and dynamic processes that result from the interaction of electromagnetic

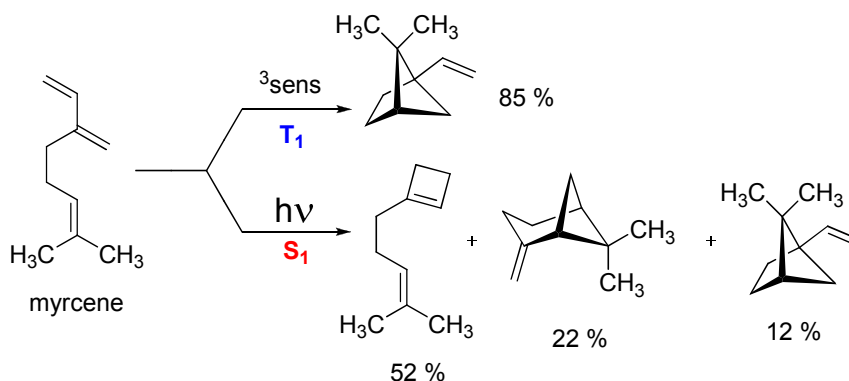
radiation with organic molecules [17]. The most important classes of organic compounds, which may be photo-reactive, can be narrowed down to: *carbonyl compounds; olefins; enones and dienones; aromatic molecules* and some *supramolecular structures* [17].

Although organic photochemistry is still underappreciated and underutilized by the synthetic community, it can be an excellent tool to fashion topologically unique scaffolds in an elegant manner. It is a different approach, allowing the preparation of scaffolds which cannot be made easily through “ground state” chemistry.

One of the striking features of photochemical reactions is the fact that singlets can react differently from triplets.

2.2.1 Triplet (sensitized) versus Singlet (direct) irradiation.

The photochemical behavior of *myrcene* showed the contrast between direct and sensitized reactions [18]. Direct irradiation of *myrcene* gives at least seven products. Three major compounds were identified (Scheme 13). However, when it is irradiated in the presence of a variety of photosensitizers (acetophenone, benzophenone, triphenylene, benzil, 9-fluorenone, etc), the formation of a single product was observed (Scheme 13):

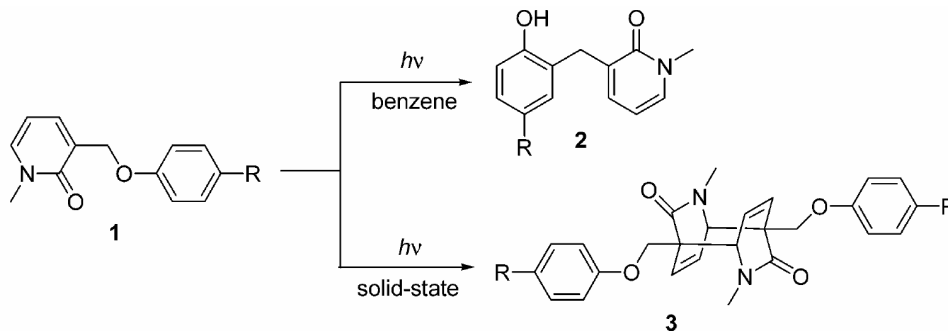


Scheme 13. Photoaddition of *myrcene* upon direct and sensitized irradiations [18].

This case illustrates not only the differences between the chemical properties of excited singlets (S) and triplets (T), but also shows that intersystem crossing from S_1 of dienes to the T_1 must be inefficient. In addition, it is an example of the “*rule of five*” – the general preference of 5- over 4- and 6-membered rings in a radical cyclization [17].

2.2.2 Phase-selective photochemical reactions.

Phase-selective photoreactions provide another opportunity to alter the outcome of a photochemical process. For instance, irradiation of 2-pyridones (**1.14**) in benzene produced rearranged products (**2.14**) with 30-40% yield through a photo-[1,3] migration of pyridine methylene group [19]. However, intermolecular [4 + 4] photocycloaddition occurred quantitatively in the solid state, yielding photodimers (**3.14**) (Scheme 14):



Scheme 14. Photochemical reaction of 2-pyridone derivatives [19].

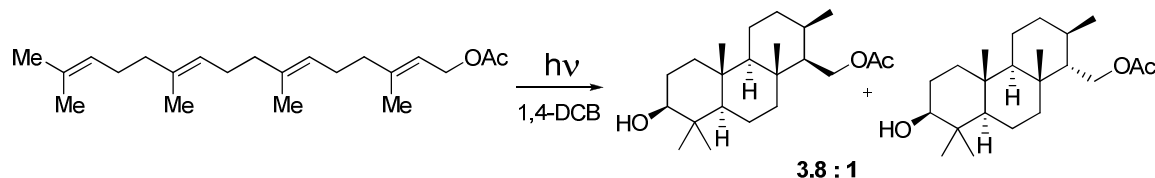
An effective π - π stacking and dipole-dipole interaction between two pyridone moieties might play central roles in an efficient configuration of precursors (**1.14**) (compound **1**, Scheme 14) for photo-dimerization in their crystal structures.

2.2.3 Synthetic application of photochemistry.

Photochemistry more frequently finds its relevance in synthetic organic chemistry. In some cases it can significantly shorten a total synthesis and quite often

complex, polycyclic or highly functionalized structures can be obtained from simple steps [20].

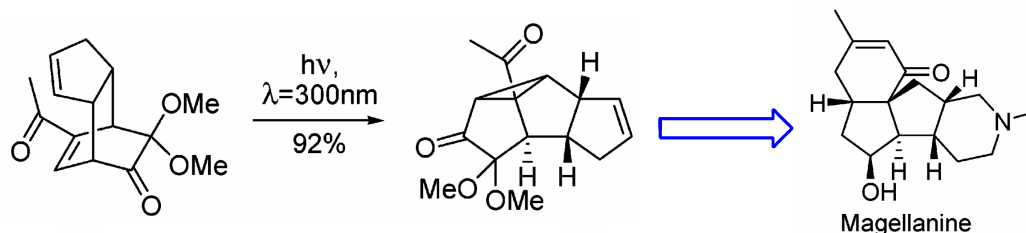
A remarkable cascade reaction was observed, when a terpene-derivative was irradiated in the presence of an electron acceptor 1,4-dicyanobenzene (1,4-DCB) and sodium dodecyl sulfate (micellar medium) as shown in Scheme 15:



Scheme 15. Sensitized intramolecular cascade cyclization of a polyene [21].

Despite the low yields (20 - 25%), these results are outstanding since the regio- and stereo-selective incorporation of water together with the formation of *trans*-ring fusions mimics characteristics of *bio*-derivation of terpenes. From a mechanistic point of view, the products could be derived from free-radical-type or ionic cyclizations [21].

A range of complex polycyclic alkaloids can be synthesized through *oxa-di- π -methane* rearrangement (ODPM) [22]. *Magellanine* is one of the alkaloids which has been isolated from club mosses. Its polycyclic framework became accessible by a method which included the *Diels-Alder* reaction of a masked *o*-benzoquinone followed by ODPM rearrangement (Scheme 16):



Scheme 16. Synthesis of Magellanine through ODPM rearrangement [22].

Irradiation of the *Diels-Alder* adduct in acetone with fluorescent lamps (RUL-3000 Å) through Pyrex filters in a Rayonet reactor afforded the tetracyclic diketone through the ODPM rearrangement in excellent yield.

An extraordinary example of the application of [2+2] photocycloaddition as a key step in the total synthesis of *Ginkgolide B* was reported by Crimmins and co-workers in 2000 [23]. Ginkgolides (Figure 6) were first isolated in 1932 from *Ginkgo biloba*. It is one of the oldest surviving plants with ancestors dating to 230 million B.C. This unique tree, which flourished in the Jurassic Period, is also known as a “living fossil”.

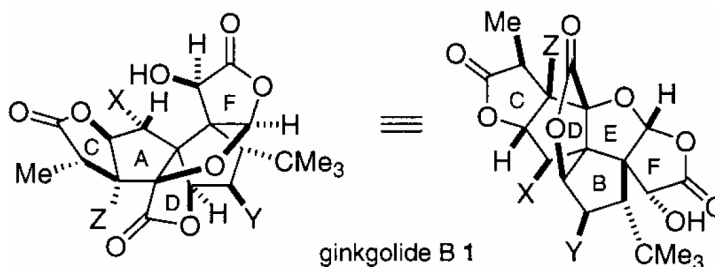
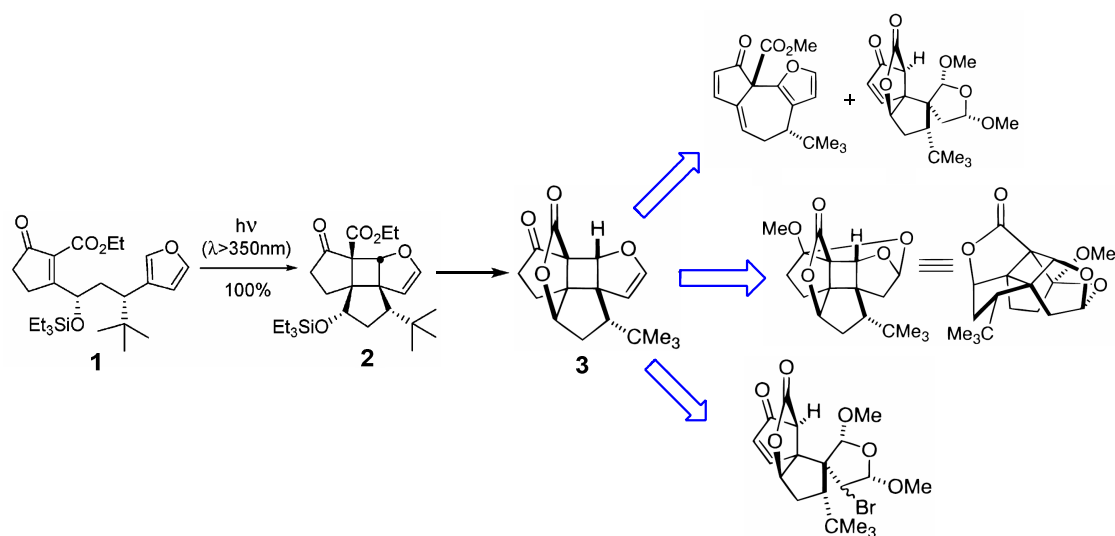


Figure 6. Ginkgolide B 1 ($X = OH$, $Y = H$, $Z = OH$), first isolated from the root bark by Furukawa in 1932 [23].

Because of the complex molecular architecture of ginkgolide B, it is an intimidating challenge for chemical synthesis. The molecule contains six rings, eleven stereogenic centers, ten oxygenated carbons, an unusual *tert*-butyl group and four tertiary carbon atoms. The congested core of the molecule was constructed through a stereoselective intramolecular photocycloaddition on enone (**1.17**). Based on the analysis of substituent effects in numerous model systems it was predicted that irradiation of cyclopentenone (**1.17**) in hexanes at >350 nm would furnish a single diastereomeric photocycloadduct (**2.17**) in quantitative yield (compound **2**, Scheme 17):



Scheme 17. Stereoselective intramolecular photocycloaddition of enone (**1.17**) [23].

It should be noticed that the next required step was the installation of the D ring bridged lactone (**3.17**). Then a series of structural diversification reactions with (**3.17**) was investigated (Scheme 17). Even though the compounds obtained from (**3.17**) were just intermediates, this example is a good illustration to how a photochemical reaction can be utilized as a key step in the construction of structurally unique scaffolds.

C. Combinatorial synthesis.

Combinatorial synthesis (along with DOS) has been one of the most rapidly developing fields in the pharmaceutical industry. Now it is an important tool in the discovery and development of new drugs. Unlike DOS, combinatorial synthesis is conditioned to create structurally related compounds with high yields. Usually this is done on a very small scale. Combinatorial synthesis can be performed either in a **parallel** fashion – a single product is obtained in each different reaction flask, or the process can be planned in such a way that **mixtures** of different molecules are produced in each reaction vessel [1].

1. Methods of parallel synthesis.

1.1 Houghten's teabag procedure.

A general method for rapid solid-phase synthesis of large numbers of peptides, known today as the “*teabag procedure*”, was first described by Richard Houghten in 1985 [24]. Standard polymeric support resin (50-100 mg) is enclosed in polypropylene 74 μm mesh packets with estimated dimensions of 15 x 20 mm (Figure 7). Then a number is placed at the top of the unsealed bag, the packet is closed and the number is permanently sealed into the polypropylene to give a clear label for each bag. After that the teabags are placed in different containers and various amino acids are added to each bottle. Deprotection and washing can be carried out in one vessel and the teabags are then redistributed between the bottles for the addition of a second amino acid, etc.

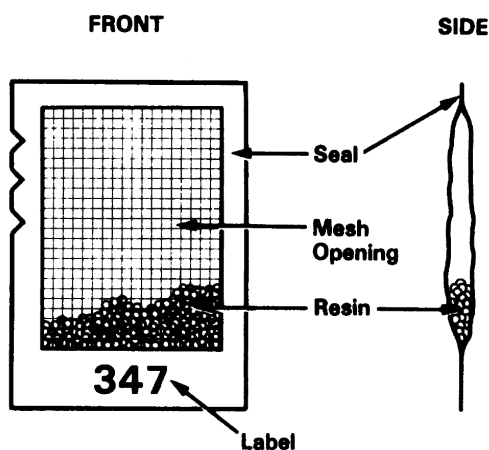


Figure 7. An example of a mesh packet containing resin [24].

By using this method, 10-20 mg of 248 different 13-residue peptides representing single amino acid variants of a segment of the hemagglutinin protein (HA1) have been prepared and characterized in less than 4 weeks.

The advantage of this approach is that it is cost-effective and does not require expensive equipment. The major weakness is the fact that it is manual and this limits the quantity and efficiency with which new compounds can be synthesized. Therefore, automatic or semi-automatic methods are more preferred for parallel synthesis [1].

1.2 Automated parallel synthesis.

Automated and semi-automated synthesizers can cope with parallel synthesis [1]. The addition of solvents and reagents can be performed automatically using syringes. Automated work-up procedures are also possible. Reactions can be carried out under inert atmosphere, heated or cooled as required.



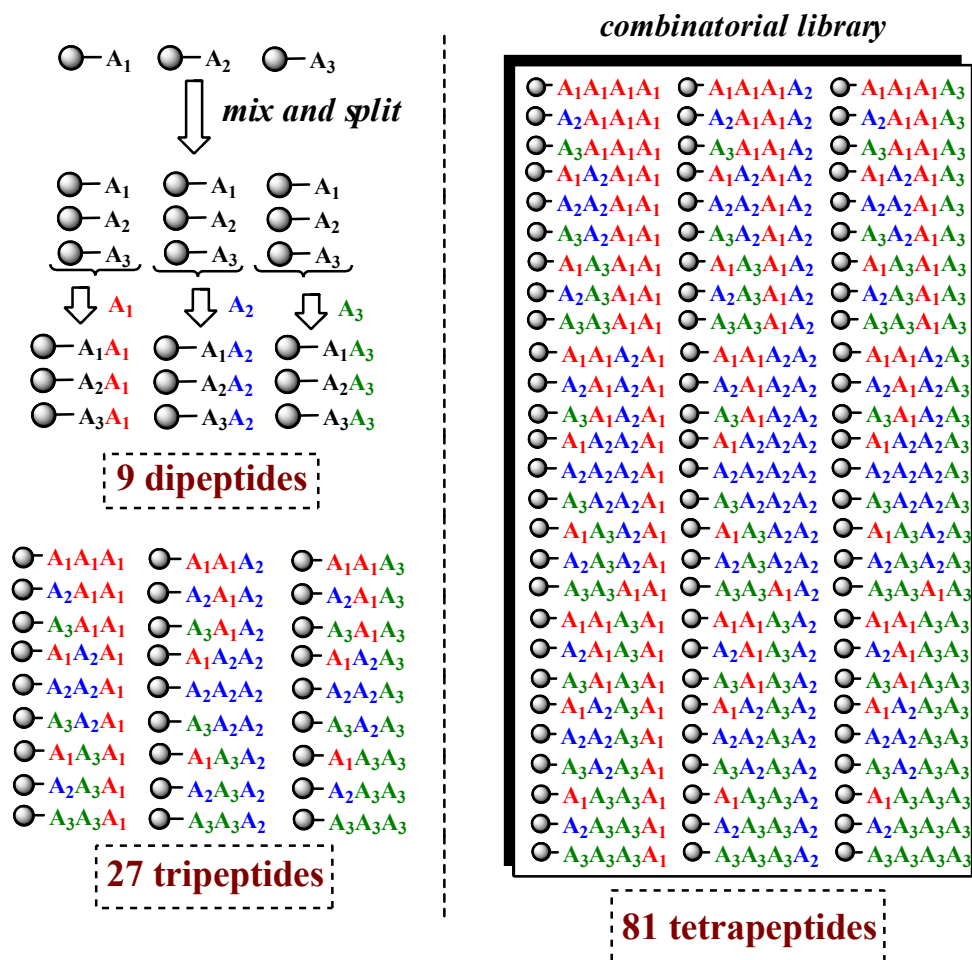
Figure 8. Titan-357 peptide synthesizer.

Automated synthesizers are designed to be multifunctional. For example, the Titan-357 peptide synthesizer (Figure 8) can not only prepare up to 36 separate peptides simultaneously in 36 reaction wells of the reactor assembly, but also produce hundreds of thousands to millions of peptides via the "mix-and-split" method.

2. Mixed combinatorial synthesis.

Combinatorial synthesis is often designed to produce a mixture of products. All the mixtures resulting from a combinatorial synthesis can be stored and referred to as *combinatorial (compound) libraries* [1]. To produce large quantities of various structures, it is important to minimize the effort involved.

The “*split-and-mix*” method, first described by Furka in 1991, is a clever way of achieving this goal. Using this approach, a library of 81 tetrapeptides can be efficiently synthesized from just three different amino acids (A_1 , A_2 and A_3). First, each amino acid needs to be linked to a solid support (see Scheme 18 - each sphere represents a resin bead with an appropriate linker). Then the beads are mixed together and separated into three equal portions. Each portion is exposed to another set of the three amino acids. After isolation of all the beads, mixing them together and splitting into three equal portions each portion contains all nine possible dipeptides (not shown on Scheme 18). Next, each set of dipeptides can react with one of the three amino acids to produce 27 different tripeptides. After another split-and-mix cycle a library of 81 tetrapeptides can be synthesized in just four experiments (Scheme 18).



Scheme 18. An illustration of the split-and-mix (split-and-pool) method.

Combinatorial libraries containing millions of compounds can be stored and later analyzed by the *high-throughput screening* technique to find an active compound, antibody or a gene. This methodology is especially popular in drug discovery and development.

D. Dynamic combinatorial chemistry.

Dynamic combinatorial chemistry (DCC) is another discipline of combinatorial chemistry. Even though it is an alternative to the classic “mixed” combinatorial synthesis, this development occupies its own important niche. In a dynamic combinatorial library

(DCL) all constituents are in equilibrium, which requires the interconversion of library members into one another through reversible chemical processes involving (a) covalent bonds or (b) non-covalent interactions (hydrogen and coordinative bonding) [25].

1. General concept.

DCC relies on the selection of the most thermodynamically stable product from an equilibrating mixture. This concept was first utilized in the 19th century in the studies of Emil Fischer on carbohydrates and of Werner on coordination complexes.

The key element of DCC is the reversible reaction that mediates the exchange of the building blocks between the library members. Reversible reactions have to meet a number of requirements: (a) it needs to be reversible on a reasonable time scale; (b) the reversible reaction needs to be compatible with the experimental conditions of the selection process, the functional groups, the solvent, and the pH; (c) reaction conditions should be mild, so as to not interfere with the fragile non-covalent interactions; (d) it needs to guarantee the solubility of all the library members at equilibrium; (e) it should be possible to “turn off” the reaction in order to isolate and characterize several selected library members; (f) ideally all library members need to be isoenergetic in order to prevent the production of reaction mixtures that are strongly predisposed toward certain products [25].

One important application is the recognition or selection of the most stable structure in mixtures of structures with different conformational properties or foldamers (Figure 9a). The structures with the most favorable internal non-covalent interactions will be stabilized and assembled in preference over those members that do not have such stabilization.

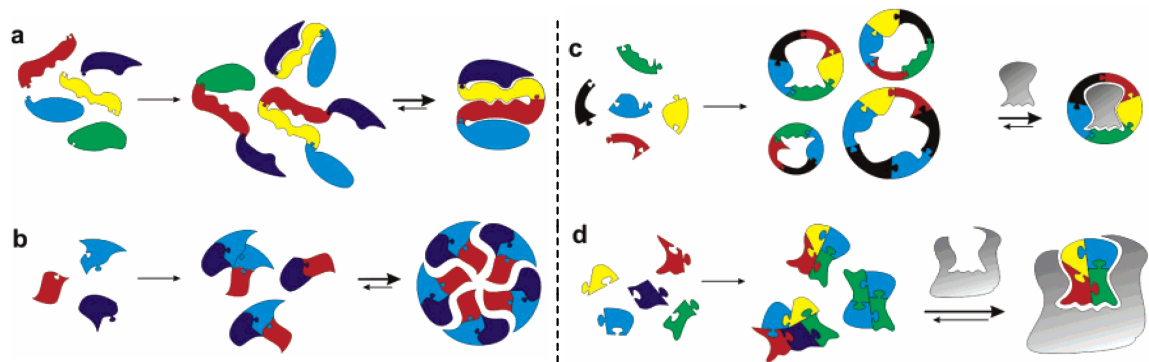


Figure 9. Different ways of selecting specific members of a DCL [25].

The stabilization of particular library members can occur through intermolecular non-covalent interactions between other members; the library composition is biased toward those members that create stable assemblies or aggregates (Figure 9b). Templating can be used to select structures that act as hosts or receptors (Figure 9c), as well as for the discovery of new guests or ligands (Figure 9d). Although there are different approaches to select a specific member of a DCL, in all cases one general principle is applied - the compound that is most stabilized through non-covalent interactions tends to be amplified in preference over other library members [25].

2. Synthetic application.

A remarkable example of a DCL was reported in 2005 by Sanders and co-workers [26]. They discovered that acetylcholine (a neurotransmitter) acts as a template to amplify [2]-catenanes from small peptide-hydrazone building blocks (**1.19**) (structure **1**, Scheme 19). Library development was initiated by the addition of trifluoroacetic acid to a solution of the building block (**1.19**) in 95:5 chloroform/DMSO. HPLC analysis revealed that linear intermediates were formed in several minutes, transforming over the

The reaction scheme illustrates the synthesis and conformational isomerization of a macrocyclic peptide. The starting material (1) is a linear peptide with a complex side chain, including a 4-methoxyphenyl group and a 1-phenyl-2-((2-oxo-1-((4-methoxyphenyl)carbamoyl)pyrrolidin-1-yl)ethoxy)ethan-1-one moiety. The reaction conditions are Ach, TFA, and CHCl₃/DMSO. The product (2) is a macrocyclic peptide. The diagram shows the conformational isomerization of the macrocycle (2) into a series of isomers (3, 4, 5, 6, 7) and finally a set of diastereomers.

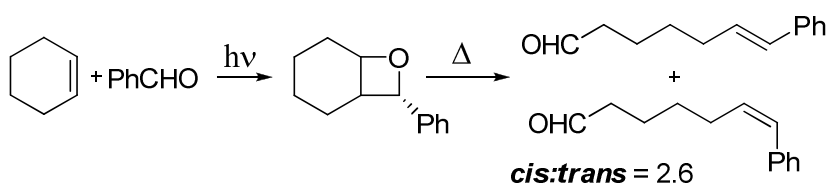
Next, acetylcholine chloride was added to the solution to serve as a template. Initially the cyclic dimer (**2.19**) was amplified, becoming the major product of the library and within an hour a new product (**7.19**) was formed at the expense of all the other members in the library. This compound was not observed in the absence of acetylcholine. Compound (**7.19**) continued to build up over a period of 45 days, eventually reaching 70% of the total material in the library [26].

Chapter Two: Oxametathesis in the aromatic series

Photo-cyclization reactions can lead to prohibitively strained polycyclic scaffolds. Further transformations offer rapid access to challenging synthetic targets by utilizing the strain created previously in the photochemical step.

A. Introduction.

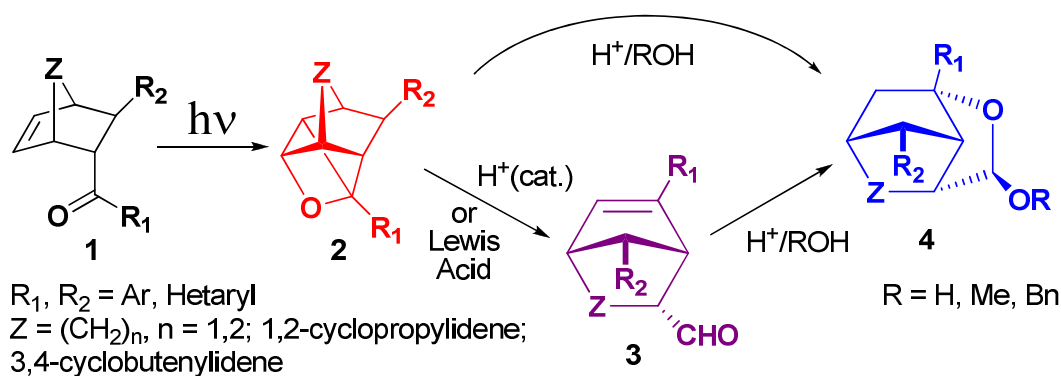
An excellent example is the *Paternò-Büchi* reaction in acylnorbornenes, studied by Rawal, where a radical fragmentation of strained polycyclic oxetanes yielded di- and triquinanes [27]. Guilford Jones in 1973 first observed that oxetanes can also be converted pyrolytically to an alternative pair of an alkene and an aldehyde. This conversion represents a *carbonyl-olefin metathesis* (proposed by Jones [28]):



Much later, in 2006, Griesbeck observed a similar reaction, which occurred via an electron transfer-induced mechanism [29]. The majority of pyrolytic transformations occur under harsh conditions with low yields, that is why they are not applicable for labile polyfunctional compounds. Only one example of milder TsOH-catalyzed reaction was reported by Jones [28]. Although such *oxametathesis* showed a synthetic potential, it was neglected for four decades.

B. Results and discussion.

We hypothesized that if the oxetane motif was a part of a strained polycycle, the fragmentation could occur under exceptionally mild conditions. We discovered a high-yielding two-step sequence, where the oxametathesis is induced by a very mild acid-catalyzed reaction in strained oxetanes **2**, affording novel polycyclic aldehydes **3** or their (hemi)acetals **4** (Scheme 20) [30]:

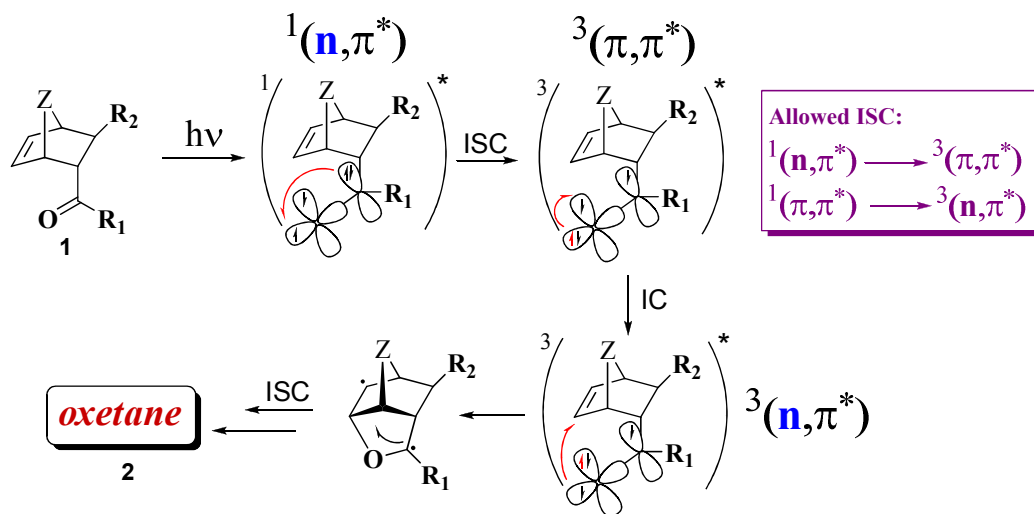


Scheme 20. Photoprotolytic oxametathesis in polycyclic systems [30].

Many kinds of (het)aryl polycycloalkenes are available via the *Diels-Alder* (*D.-A.*) addition of heterocyclic chalcones [31] and other benzoyl ethylenes to a variety of dienes. The *Paternò-Büchi* step is the most critical part of the synthesis. This is where the strain in the polycyclic oxetane is captured. The *Paternò-Büchi* [2+2] cycloaddition is forbidden in the ground state and can only occur in the excited state. Thus it requires a UV source of irradiation which is capable of exciting the aryl group into its $n \rightarrow \pi^*$ excited state and eventually produce an oxetane, decorated by a variety of heterocyclic pendants. With such abundance of oxetane precursors, this oxametathesis sequence

allows for fast access to structures **4** having diverse polycyclic cores decorated by a variety of heterocyclic pendants (Scheme 20).

In general, irradiation of ketones **1** in benzene with a UV source, is conditioned to excite the aromatic carbonyl groups into their singlet (S_1) $n \rightarrow \pi^*$ excited state. In many cases the reaction is not concerted but stepwise occurring via a triplet (T_1) $n \rightarrow \pi^*$ excited state [17]. Since the transition from S_1 ($n \rightarrow \pi^*$) to T_1 ($n \rightarrow \pi^*$) is forbidden, intersystem crossing (ISC) must occur first to T_2 ($\pi \rightarrow \pi^*$) and then via internal conversion (IC) a reactive and more stable T_1 ($n \rightarrow \pi^*$) is formed. The formation of a 1,4-diradical and another ISC leads to oxetanes with > 97% yield in most of the cases (Scheme 21):

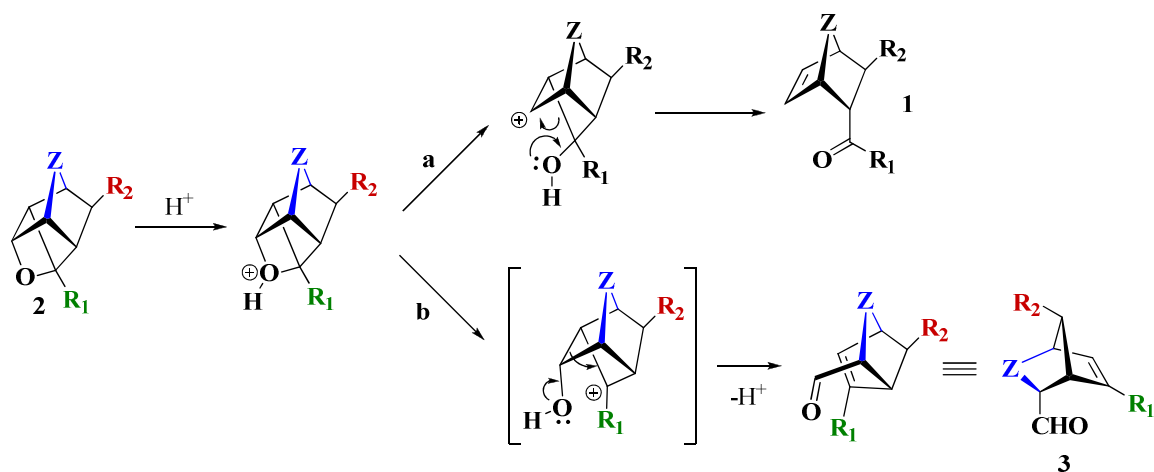


Scheme 21. A mechanism of the *Paternò-Büchi* reaction [17].

Both the *Paternò-Büchi* step **1**→**2** and the cycloreversion **2**→**3**→**4** are remarkably clean reactions [30].

The mechanism of the protolytic metathesis **2**→**3** (oxetane → aldehyde) involves protonation of the polycyclic oxetane. There are two possibilities for fragmentation

(Scheme 22): either pathway **(a)** the retro-*Paternò-Büchi* reaction involving the formation of a secondary carbocation and further reaction producing started materials or pathway **(b)** the *oxametathesis* involving formation of a tertiary carbocation and further *Grob*-like fragmentation. In order for the *Grob*-like fragmentation to occur (pathway **b**), the aryl substituent (R_1) in the oxetane must not destabilize the benzylic carbocation. This mechanism imposes only one constraint on the nature of the *endo*-aryl group R_1 , which had to be an Electron Releasing (Donating) Group (ERG). In cases where R_1 was an Electron Withdrawing Group (EWG), either the reaction was not observed or a *retro-Paternò-Büchi* opening took place (pathway **a**):



Scheme 22. A plausible mechanism of the **2** → **3** step: **(a)** the retro-*Paternò-Büchi* reaction or **(b)** oxametathesis.

This two-step **1**→**3** conversion can also be implemented as a *one-pot* transformation, with the fragmentation being effected by a trace amount of HCl present in solvents such as chloroform or DCM. In most cases, aldehydes **3** form when the precursors **1** are irradiated in reagent grade CH_2Cl_2 . With more HCl added, a secondary

electrophilic addition to the newly formed styrene double bond of **3** takes place, yielding hemiacetals **4** as a result of the formyl participation. Lewis acids, such as boron trifluoride, promote oxetane transformation into aldehydes **3** but do not allow for the hemiacetal formation. Protic acids in the presence of water furnish hemiacetals in most cases.

Variations in the carbocyclic framework slightly modulate the reactivity. *D*.-*A*. adducts **1rs** of cycloheptatriene, with a tricyclo[3.2.2.0^{2,4}]nonane core, form oxetanes **2rs**, which are stable at room temperature in the presence of HCl. However, they are converted into aldehydes **3rs** via a BF₃-catalyzed reaction as shown in Figure 10:

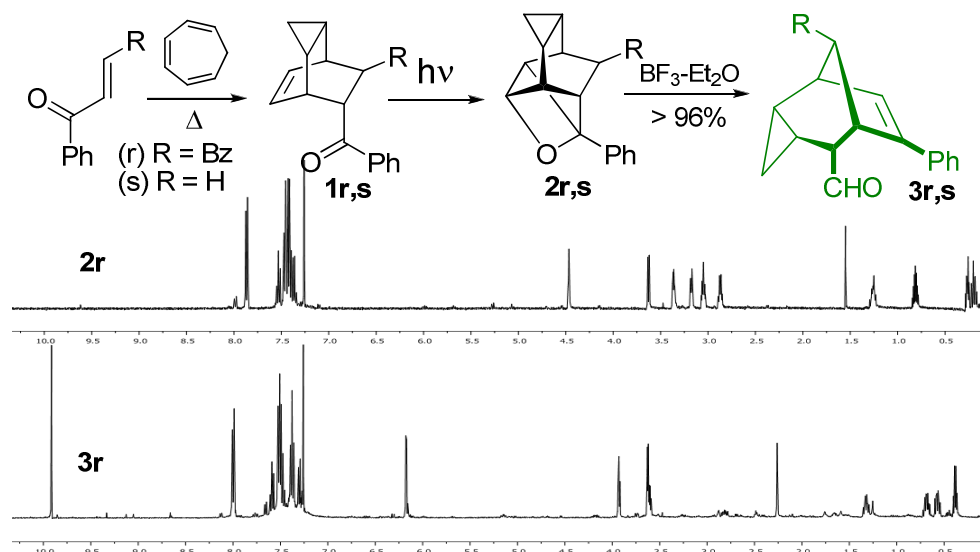
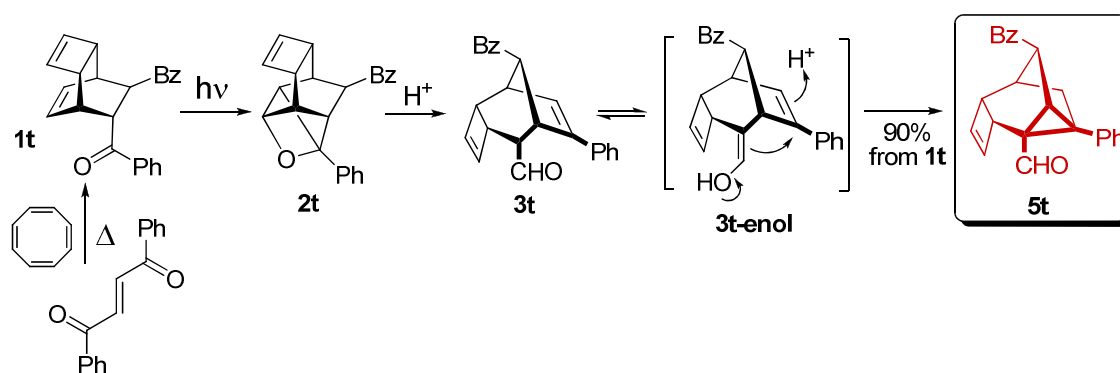


Figure 10. Transformation of **2r** to **3r** as followed by NMR [30].

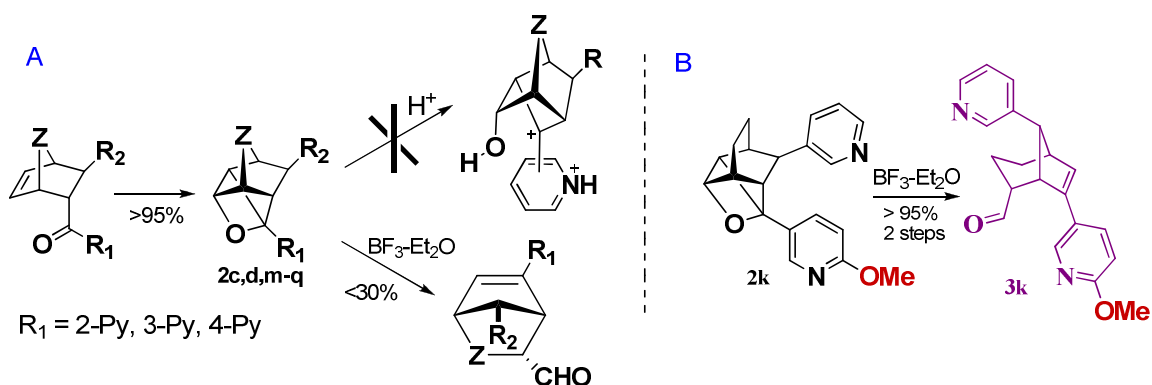
The starting oxetane **2r** (top spectrum) is cleanly converted into the aldehyde **3r** upon addition of BF₃·OEt₂. The bottom spectrum is a snapshot of the reaction mixture without purification.

Oxametathesis of oxetane **2t** derived from the 1:1 adduct of dibenzoyl ethylene and cyclooctatetraene (COT) **1t** yields aldehyde **3t** (Scheme 23). However, upon further acidolysis, **3t** did not cyclize into a hemiacetal but rather produced formylcyclopropane **5t**. A plausible mechanism for the formation of **5t** involves the enol moiety in **3t-enol** acting as an internal nucleophile. The conversion of **3t** into **5t** was approximately 90% with 10% of residual **3t** remaining in the reaction mixture.



Scheme 23. Oxametathesis of **2t** derived from dibenzoyl ethylene and COT [30].

As expected, pyridyl oxetanes **2c,d,m-q** (Scheme 24A) rearrange into aldehydes **3** only with modest yields (< 30%). Protic acids (HCl, TsOH, TfOH), even upon heating, do not effect the transformation in this series due to protonation of the pyridine moiety and further destabilization of the carbocation. However, the introduction of an electron-donating methoxy group in the *para*-position, as in **2k**, suppresses the destabilizing effect of the pyridyl and restores the reactivity: **2k** undergoes BF_3 -catalyzed rearrangement yielding aldehyde **3k** (95% yield over two steps, Scheme 24B).



Scheme 24. Oxametathesis of *endo*-pyridyl oxetanes (A) **2c,d,m-q**; (B) **2k** [30].

To summarize, we have developed a new, experimentally simple, high-yielding photoinduced transformation of readily available diverse starting materials into polycyclic aldehydes and their (hemi)acetals decorated with various pendants. This methodology offers an expeditious increase of molecular complexity and diversity of the target scaffolds.

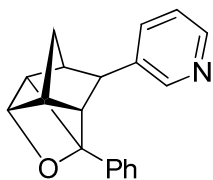
C. Experimental section.

Common solvents were purchased from Pharmco and used as is, except for THF, which was refluxed over and distilled from potassium benzophenone ketyl prior to use. Common reagents were purchased from Aldrich or TCI America and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz or Varian Mercury 400 MHz instrument in CDCl₃ with TMS as an internal standard (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument (see Appendix A). High resolution mass spectra were obtained on the MDS SCIEX/Applied Biosystems API QSTARTM Pulsar i Hybrid LC/MS/MS System mass spectrometer by Dr. Shuji Kato from the University of Colorado

at Boulder. For the synthetic details, ^1H , ^{13}C , COSY NMR spectra see supporting information [30].

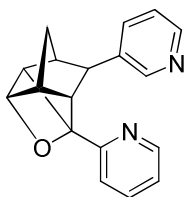
1. Preparation of the *Paternò-Büchi* adducts (2):

Approximately 0.1 M solution of an *endo*-precursor **1** in benzene (or other specified solvent) was irradiated in Pyrex vials in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) or a UVLED-based illuminator with five 250 mW @ 365 nm Nichia chips. Irradiation resulted in a quantitative conversion to oxetanes **2**, which were used without further purification. Crystalline oxetanes were recrystallized and their X-Ray structures obtained. NOTE: We attempted to further purify reaction mixtures by chromatography. The strained polycyclic oxetanes are not stable on silica gel, producing various amounts of aldehydes **3** via oxametathesis.



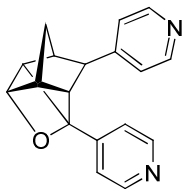
4-Phenyl-7-(3-pyridyl)-3-oxatetracyclo[4.2.1.0^{2,5}.0^{4,8}]nonane (2b): A

solution of 40 mg of *trans-endo*-2-benzoyl-3-(3-pyridyl)bicyclo[2.2.1]hept-5-ene in 40 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ^1H NMR (400 MHz, CDCl_3) δ = 8.60 (m, 1H), 8.48 (m, 1H), 7.90 (m, 1H), 7.50-7.36 (m, 6H), 4.48 (dd, J = 3.7, 2.2 Hz, 1H), 3.64 (dddd, J = 3.8, 3.8, 1.8, 1.8 Hz, 1H), 3.34 (m, 1H), 3.19 (ddd, J = 4.3, 2.1, 2.1 Hz, 1H), 3.00 (m, J = 4.1, 2.1 Hz, 1H), 2.34 (m, 1H), 1.62 (dd, J = 11.3, 2.4 Hz, 1H), 1.53 (dd, J = 11.3, 2.4 Hz, 1H).



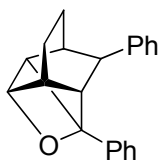
4-(2-Pyridyl)-7-(3-pyridyl)-3-oxatetracyclo[4.2.1.0^{2,5}.0^{4,8}]nonane (2c):

A solution of 100 mg of *trans-endo*-2-(2-pyridoyl)-3-(3-pyridyl)bicyclo[2.2.1]hept-5-ene in 40 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ¹H NMR (400 MHz, CDCl₃) δ = 8.60 (d, *J* = 4.8 Hz, 1H), 8.48 (d, *J* = 2.3 Hz, 1H), 8.45 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.72 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.51 (t, *J* = 8.2 Hz, 2H), 7.23 (m, 2H), 4.86 (dd, *J* = 3.7, 2.3 Hz, 1H), 3.90 (m, 1H), 3.70 (dddd, *J* = 3.7, 3.7, 1.8, 1.8 Hz, 1H), 3.22 (ddd, *J* = 4.1, 2.0, 2.0 Hz, 1H), 3.01 (dddd, *J* = 4.0, 4.0, 2.1, 2.1 Hz, 1H), 2.41 (m, 1H), 1.64 (dd, *J* = 11.4, 2.7 Hz, 1H), 1.55 (dd, *J* = 11.4, 2.6 Hz, 1H).

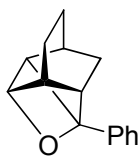


4,7-Bis(4-pyridyl)-3-oxatetracyclo[4.2.1.0^{2,5}.0^{4,8}]nonane (2d):

A solution of 100 mg of *trans-endo*-2-(4-pyridoyl)-3-(4-pyridyl)bicyclo[2.2.1]hept-5-ene in 40 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ¹H NMR (400 MHz, CDCl₃) δ = 8.65 (d, *J* = 5.9 Hz, 2H), 8.52 (d, *J* = 5.8 Hz, 2H), 7.35 (d, *J* = 5.9 Hz, 2H), 7.09 (d, *J* = 5.8 Hz, 2H), 4.86 (dd, *J* = 3.8, 2.2 Hz, 1H), 3.62 (dddd, *J* = 3.8, 3.8, 1.9, 1.9 Hz, 1H), 3.30 (m, 1H), 3.16 (ddd, *J* = 4.0, 1.8, 1.8 Hz, 1H), 3.02 (m, 1H), 2.40 (m, 1H), 1.59 (m, 2H).

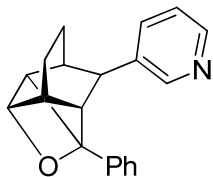


4,7-Diphenyl-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2e): A solution of 0.29 g of *trans-endo*-2-benzoyl-3-phenylbicyclo[2.2.2]oct-5-ene in 50 mL of benzene or DCM (the presence of HCl in DCM induces metathesis) (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ¹H NMR (400 MHz, CDCl₃) δ = 7.49 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.37 (m, *J* = 7.9, 1.4 Hz, 2H), 7.34-7.30 (m, 1H), 7.30-7.27 (m, 4H), 7.19 (m, 1H), 4.53 (dd, *J* = 3.8, 1.7 Hz, 1H), 3.62 (dddd, *J* = 5.5, 3.5, 1.6, 1.6 Hz, 1H), 3.30 (d, *J* = 6.7 Hz, 1H), 3.20-3.15 (d, *J* = 6.6 Hz, 1H), 2.70 (m, 1H), 2.46-2.38 (m, *J* = 6.2, 3.9, 1.9, Hz, 1H), 1.64 (dtd, *J* = 14.2, 10.1, 1.9 Hz, 1H), 1.55-1.39 (m, *J* = 17.4, 13.5, 10.2, 4.1 Hz, 2H), 1.14 (m, 1H). ¹H NMR (400 MHz, benzene-d₆) δ = 7.49 (dd, *J* = 7.5, 1.6 Hz, 2H), 7.15-6.96 (m, 8H), 4.28 (dd, *J* = 3.6, 1.9 Hz, 1H), 3.34 (dddd, *J* = 5.5, 3.4, 1.5, 1.5 Hz, 1H), 3.29-3.22 (d, *J* = 6.7 Hz, 1H), 3.05 (m, 1H), 2.56 (m, 1H), 2.01-1.92 (m, 1H), 1.62-1.46 (dddd, *J* = 13.8, 9.7, 9.7, 2.1 Hz, 1H), 1.33 (ddd, *J* = 13.4, 9.8, 4.2 Hz, 1H), 1.17-1.04 (ddd, *J* = 13.9, 10.2, 3.8 Hz, 1H), 0.79 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 141.65, 137.53, 128.70, 128.56, 128.19, 127.97, 127.48, 125.84, 97.85, 82.77, 57.84, 48.09, 45.68, 39.51, 32.81, 20.64, 18.01.



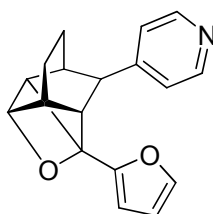
4-Phenyl-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2f): A solution of 0.21 g of *endo*-2-benzoylbicyclo[2.2.2]oct-5-ene in 50 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ¹H NMR (400 MHz, CDCl₃) δ = 7.49-7.28 (m, 5H), 4.56-4.44 (dt, *J* = 3.7, 1.3 Hz, 1H), 3.36 (dddd, *J* = 5.5, 3.5, 1.7, 1.7 Hz, 1H), 2.55

(m, 2H), 2.04-1.86 (m, 2H), 1.74 (m, 2H), 1.60 (dddd, $J = 12.8, 9.65, 4.6, 1.0$ Hz, 2H), 1.21 (m, 1H).



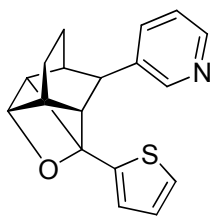
4-Phenyl-7-(3-pyridyl)-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2g): A

solution of 100 mg of *trans-endo*-2-benzoyl-3-(3-pyridyl)bicyclo[2.2.2]oct-5-ene in 40 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. (The product also could be purified on a silica gel column using hexane/EtOH 5:1). ¹H NMR (400 MHz, CDCl₃) δ = 8.58 (d, $J = 1.7$ Hz, 1H), 8.46 (d, $J = 4.9$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.49-7.29 (m, 6H), 4.55 (dd, $J = 3.6, 2.0$ Hz, 1H), 3.64 (dddd, $J = 5.6, 3.5, 1.7, 1.7$ Hz, 1H), 3.27 (d, $J = 6.5$ Hz, 1H), 3.19 (d, $J = 6.5$ Hz, 1H), 2.73 (m, 1H), 2.47 (m, $J = 6.0, 6.0, 3.8, 2.0, 2.0$ Hz, 1H), 1.54-1.40 (m, 3H), 1.23 (m, 1H).



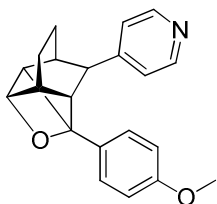
4-(2-Furanyl)-7-(4-pyridyl)-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane

(2h): A solution of 0.12 g of *trans-endo*-2-(2-furoyl)-3-(4-pyridyl)bicyclo[2.2.2]oct-5-ene in 50 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ¹H NMR (400 MHz, CDCl₃) δ = 8.54 (m, 2H), 7.45 (dd, $J = 1.8, 0.8$ Hz, 1H), 7.24 (ddd, $J = 5.0, 1.1, 1.1$ Hz, 2H), 6.49 (dd, $J = 3.3, 0.8$ Hz, 1H), 6.39 (dd, $J = 3.3, 1.8$ Hz, 1H), 4.48 (dd, $J = 3.5, 1.8$ Hz, 1H), 3.76 (dddd, $J = 5.6, 3.4, 1.6, 1.6$ Hz, 1H), 3.31-3.27 (m, 2H), 2.65 (m, 1H), 2.41 (m, 1H), 1.53-1.42 (m 3H), 1.15 (m, 1H).



7-(3-Pyridyl)-4-(2-thienyl)-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2i):

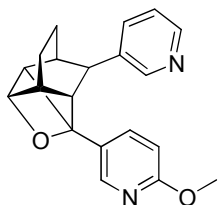
A solution of 0.35 g of *trans-endo*-2-(2-thienoyl)-3-(3-pyridyl)bicyclo[2.2.2]oct-5-ene in 50 mL of benzene (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ¹H NMR (400 MHz, CDCl₃) δ = 8.57 (m, 1H), 8.46 (m, 1H), 7.60 (m, 1H), 7.36 (m, 1H), 7.24 (m, *J* = 7.9, 4.9 Hz, 1H), 7.17 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.02 (dd, *J* = 5.0, 3.6 Hz, 1H), 4.50 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.65 (dddd, *J* = 5.7, 3.6, 1.9, 1.9 Hz, 1H), 3.40 (d, *J* = 6.7 Hz, 1H), 3.23 (d, *J* = 6.7 Hz, 1H), 2.71 (m, 1H), 2.45 (m, *J* = 6.1, 4.2, 2.0 Hz, 1H), 1.55-1.40 (m, 3H), 1.18 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 149.46, 147.43, 140.33, 136.83, 135.38, 127.25, 127.18, 127.15, 123.19, 93.31, 82.30, 60.33, 46.67, 46.46, 39.32, 32.46, 20.28, 17.80.



4-(4-Methoxyphenyl)-7-(4-pyridyl)-3-

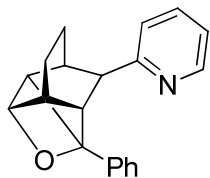
oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2j): A solution of 0.28 g of *trans-endo*-2-(4-methoxybenzoyl)-3-(4-pyridyl)bicyclo[2.2.2]oct-5-ene in 50 mL of benzene (10 mL per one glass vial) was irradiated with UV LED-365 for 72 hours. ¹H NMR (400 MHz, CDCl₃) δ = 8.51 (m, 2H), 7.42 (m, 2H), 7.20 (m, 2H), 6.91 (m, 2H), 4.50 (dd, *J* = 3.7, 1.8 Hz, 1H), 3.80 (s, 3H), 3.61 (dddd, *J* = 5.6, 3.5, 1.7, 1.7 Hz, 1H), 3.20 (d, *J* = 6.6 Hz, 1H), 3.16 (d, *J* = 6.6 Hz, 1H), 2.69 (m, 1H), 2.43 (m, 1H), 1.54-1.44 (m, 3H), 1.17 (m, 1H).

^{13}C NMR (400 MHz, CDCl_3) δ = 160.13, 151.08, 149.64, 129.06, 128.96, 123.43, 114.08, 97.46, 82.26, 57.31, 55.53, 47.79, 45.07, 39.35, 32.28, 20.55, 17.94. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{NNaO}_2^+$ (MNa^+) 342.1465, found 342.1461.



4-(4-Methoxy-3-pyridyl)-7-(3-pyridyl)-3-

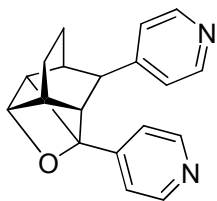
oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2k): A solution of 0.17 g of *trans-endo*-2-(4-methoxy-3-pyridoyl)-3-(3-pyridyl)bicyclo[2.2.2]oct-5-ene in 50 mL of benzene (10 mL per one glass vial) was irradiated with UV LED-365 for 72 hours. ^1H NMR (400 MHz, CDCl_3) δ = 8.56 (m, 1H), 8.45 (d, J = 4.7 Hz, 1H), 8.27 (d, J = 2.4 Hz, 1H), 7.72 (dd, J = 8.6, 2.5 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.24 (dd, J = 7.9, 4.8 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 4.53 (dd, J = 3.7, 1.8 Hz, 1H), 3.93 (s, 3H), 3.65 (dddd, J = 5.9, 3.9, 2.0, 2.0 Hz, 1H), 3.20 (d, J = 7.0 Hz, 2H), 2.71 (m, 1H), 2.44 (m, J = 6.1, 4.2, 2.0 Hz, 1H), 1.57-1.41 (m, 3H), 1.19 (m, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ = 164.55, 149.35, 147.39, 146.32, 138.05, 136.67, 135.38, 128.50, 125.43, 123.17, 111.13, 95.78, 82.74, 57.43, 53.75, 46.04, 44.79, 39.25, 32.43, 20.32, 17.77.



4-Phenyl-7-(2-pyridyl)-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2l): A

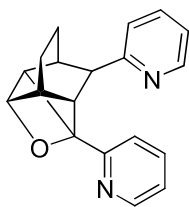
solution of 130 mg of *trans-endo*-2-benzoyl-3-(2-pyridyl)bicyclo[2.2.2]oct-5-ene in 50 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ^1H NMR (400 MHz, CDCl_3) δ = 8.60 (d, J = 4.5 Hz, 1H), 7.75 (m, 1H), 7.49 (m, J = 6.8

Hz, 2H), 7.41-7.24 (m, 5H), 4.55 (dd, $J = 3.6, 1.8$ Hz, 1H), 3.64 (dddd, $J = 5.5, 3.5, 1.6, 1.6$ Hz, 1H), 3.42 (d, $J = 6.6$ Hz, 1 H), 3.30 (d, $J = 6.6$ Hz, 1 H), 2.76 (m, 2H), 1.51 (m, 3H), 1.24 (m, 1H).



4,7-Bis(4-pyridyl)-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2m): A

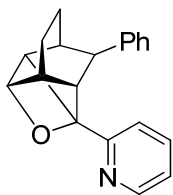
solution of 60 mg of *trans-endo*-2-(4-pyridoyl)-3-(4-pyridyl)bicyclo[2.2.2]oct-5-ene in 20 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ¹H NMR (400 MHz, CDCl₃) δ = 8.64 (m, 2H), 8.54 (m, 2H), 8.36 (m, 2H), 8.25 (m, 2H), 4.59 (dd, $J = 3.7, 1.9$ Hz, 1H), 3.63 (dddd, $J = 5.7, 3.6, 1.8, 1.8$ Hz, 1H), 3.24 (d, $J = 6.7$ Hz, 1H), 3.14 (d, $J = 6.7$ Hz, 1H), 2.75 (m, 1H), 2.51 (m, 1H), 1.55-1.48 (m, 3H), 1.23 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 150.95, 150.20, 149.26, 145.97, 123.48, 121.84, 96.02, 83.19, 57.90, 47.71, 45.97, 39.47, 32.35, 20.44, 17.65.



4,7-Bis(2-pyridyl)-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2n): A

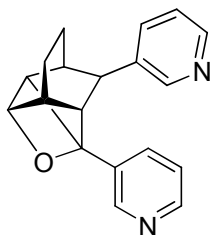
solution of 70 mg of *trans-endo*-2-(2-pyridoyl)-3-(2-pyridyl)bicyclo[2.2.2]oct-5-ene in 30 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ¹H NMR (400 MHz, CDCl₃) δ = 8.49 (m, 1H), 7.62 (ddd, $J = 7.8, 7.8, 1.8$ Hz, 1H), 7.53 (ddd, $J = 7.7, 7.7, 1.8$ Hz, 1H), 7.46 (d, $J = 7.9$ Hz, 1H), 7.23 (d, $J = 7.9$ Hz, 1H), 7.13 (dd, $J = 7.5, 5.0$ Hz, 1H), 7.03 (dd, $J = 7.4, 4.9$ Hz, 1H), 4.50 (dd, $J = 3.6, 1.8$ Hz, 1H), 3.80 (d, $J = 6.6$ Hz, 1H), 3.60 (dddd, $J = 5.6, 3.5, 1.8, 1.8$ Hz, 1H), 3.32 ($J =$

6.6 Hz, 1H), 2.68 (m, 1H), 2.55 (m, 1H), 1.52-1.40 (m, 3H), 1.12 (m, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ = 162.10, 157.95, 149.26, 149.07, 136.52, 135.90, 123.02, 122.70, 121.75, 120.92, 97.47, 83.09, 58.81, 50.64, 46.79, 39.79, 32.77, 20.93, 18.03.



4-(2-Pyridyl)-7-phenyl-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2o): A

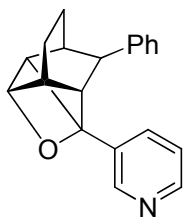
solution of 90 mg *trans-endo*-2-(2-pyridoyl)-3-phenylbicyclo[2.2.2]oct-5-ene in 30 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ^1H NMR (400 MHz, CDCl_3) δ = 8.59 (d, J = 4.9 Hz, 1H), 7.70 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.31-7.20 (m, 6H), 4.57 (dd, J = 6.6, 1.9 Hz, 1H), 3.75 (d, J = 6.8 Hz, 1H), 3.68 (dddd, J = 5.6, 3.6, 1.8, 1.8 Hz, 1H), 3.23 (d, J = 6.7 Hz, 1H), 2.71 (m, 1H), 2.51 (m, J = 6.3, 4.0, 2.0, Hz, 1H), 1.70-1.49 (m, 3H), 1.16 (m, 1H).



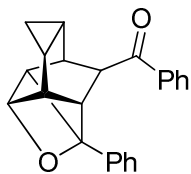
4,7-Bis(3-pyridyl)-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2p): A

solution of 0.12 g of *trans-endo*-2-(3-pyridoyl)-3-(3-pyridyl)bicyclo[2.2.2]oct-5-ene in 50 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ^1H NMR (400 MHz, CDCl_3) δ = 8.73 (dd, J = 2.3, 0.8 Hz, 1H), 8.60 (dd, J = 4.9, 1.7 Hz, 1H), 8.57 (d, J = 2.3 Hz, 1H), 7.81 (ddd, J = 7.9, 2.3, 1.7 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.33 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 7.24 (ddd, J = 7.8, 4.8, 0.9 Hz, 1H), 4.58 (dd, J = 3.6, 1.9 Hz, 1H), 3.69 (m, 1H), 3.23 (d, J = 6.9 Hz, 2H), 2.76 (m, 1H), 2.49 (m, 1H),

1.57-1.43 (m, 3H), 1.21 (m, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ = 150.22, 149.44, 148.93, 147.59, 136.44, 135.37, 134.99, 132.79, 123.60, 123.22, 95.87, 83.21, 57.67, 46.02, 45.31, 39.39, 32.52, 20.33, 17.72. HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}^+$ (MH^+) 291.1492, found 291.1488.

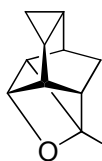


4-(3-Pyridyl)-7-phenyl-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2q): A solution of 90 mg of *trans-endo*-2-(3-pyridoyl)-3-phenylbicyclo[2.2.2]oct-5-ene in 30 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ^1H NMR (400 MHz, CDCl_3) δ = 8.74 (m, 1H), 8.57 (m, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.34-7.23 (m, 6H), 4.57 (s, 1H), 3.67 (m, 1H), 3.25 (d, J = 6.7 Hz, 1H), 3.21 (d, J = 6.7 Hz, 1H), 2.72 (m, 1H), 2.44 (m, 1H), 1.65 (m, 1H), 1.49 (m, 2H), 1.15 (m, 1H).

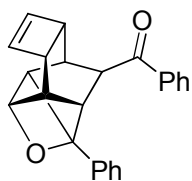


11-benzoyl-4-phenyl-3-oxapentacyclo[4.3.2.0^{2,5}.0^{4,10}.0^{7,9}]undecane (2r): A solution of 0.32 g of *trans*-8,9-dibenzoyltricyclo[3.2.2.0^{2,4}]non-6-ene in 50 mL of DCM (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. The product was purified on a silica gel column using hexane/EtOAc gradient (20:1 to 15:1). The product was obtained with 75% yield (0.24 g). ^1H NMR (400 MHz, CDCl_3) δ = 7.87 (dd, J = 7.9, 1.6 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.48-7.34 (m, 7H), 4.47 (dd, J = 2.7, 2.7 Hz, 1H), 3.63 (dd, J = 6.4, 1.2 Hz, 1H), 3.37 (dddd, J = 5.5, 3.7, 2.2, 2.2 Hz, 1H), 3.18 (dd, J = 6.3, 1.4 Hz, 1H), 3.05 (dddd, J = 6.1, 6.1, 2.2, 2.2 Hz, 1H), 2.87 (q, J

= 5.5 Hz, 1H), 1.27 (m, 1H), 0.82 (tt, $J = 8.4, 4.2$ Hz, 1H), 0.27 (ddd, $J = 6.4, 3.9, 3.9$ Hz, 1H), 0.20 (dt, $J = 7.9, 7.9, 6.3$ Hz, 1H). ^1H NMR (400 MHz, CD_2Cl_2) $\delta = 7.87$ (d, $J = 7.6$ Hz, 2H), 7.56 (t, $J = 7.2$ Hz, 1H), 7.49-7.39 (m, 7H), 4.44 (dd, $J = 2.7$ Hz, 1H), 3.63 (dd, $J = 6.5, 1.4$ Hz, 1H), 3.36 (dddd, $J = 5.5, 3.4, 2.1, 2.1$ Hz, 1H), 3.12 (dd, $J = 6.3, 1.5$ Hz, 1H), 2.98 (dddd, $J = 6.1, 6.1, 2.2, 2.2$ Hz, 1H), 2.88 (q, $J = 5.5$ Hz, 1H), 1.22 (dddd, $J = 8.0, 8.0, 6.0, 3.8$ Hz, 1H), 0.80 (tt, $J = 8.4, 4.3$ Hz, 1H), 0.28 (dt, $J = 6.2, 3.9, 3.9$ Hz, 1H), 0.19 (dt, $J = 7.9, 7.9, 6.4$ Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) $\delta = 200.10, 136.98, 136.88, 133.15, 129.05, 128.90, 128.86, 128.06, 127.45, 96.29, 83.29, 56.99, 56.56, 46.55, 37.82, 35.96, 14.41, 7.82, 4.03$. ^{13}C NMR (400 MHz, CD_2Cl_2) $\delta = 200.20, 137.55, 137.41, 133.35, 129.18, 129.05, 128.87, 128.30, 127.77, 96.42, 83.44, 57.33, 56.86, 47.00, 38.27, 36.16, 14.66, 8.07, 4.06$.



4-Phenyl-3-oxapentacyclo[4.3.2.0^{2,5}.0^{4,10}.0^{7,9}]undecane (2s): A solution of 0.17 g of *endo*-8-benzoyltricyclo[3.2.2.0^{2,4}]non-6-ene in 50 mL of benzene (10 mL per one glass vial) was irradiated with UV LED-365 for 24 hours. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.92$ (m, 2H), 7.52–7.27 (m, 3H), 4.44 (dd, $J = 2.81$ Hz, 1H), 3.15 (dddd, $J = 5.42, 3.55, 1.90, 1.90$ Hz, 1H), 2.79 (dddd, $J = 6.02, 6.02, 2.11, 2.11$ Hz, 1H), 2.60 (m, $J = 6.23$ Hz, 1H), 2.24 (m, $J = 5.51$ Hz, 1H), 1.85 (ddd, $J = 11.44, 6.34, 1.56$ Hz, 1H), 1.65 (dd, $J = 11.50, 2.02$ Hz, 1H), 1.30 (m, 1H), 1.19 (m, 1H), 0.29 (m, 2H).



12-Benzoyl-4-phenyl-3-oxapentacyclo[4.4.2.0^{2,5}.0^{4,11}.0^{7,10}]dodec-8-ene

(2t): A solution of 1.41 g of *trans*-7,8-dibenzoyltricyclo[4.2.2.0^{2,5}]deca-3,9-diene (4.14 mmol) in 10 mL of DCM (1 mL per one quartz or glass vial) was irradiated with RPR-3000 or UV LED-365 (in case of RPR-3500 reaction occurs slower) for 48 hours. The eluent is ethyl acetate/hexane, 1:30 (initially), and then 1:20. The product was obtained with 34% yield (0.48 g). ¹H NMR (400 MHz, CDCl₃) δ = 7.82 (dd, *J* = 7.4, 1.5 Hz, 2H), 7.55-7.48 (m, 3H), 7.44-7.35 (m, 5H), 6.14 (d, *J* = 2.6 Hz, 1H), 5.93 (ddd, *J* = 2.7, 1.3, 1.3 Hz, 1H), 4.84 (dd, *J* = 3.2, 1.9 Hz, 1H), 3.67 (dd, *J* = 7.0, 1.5 Hz, 1H), 3.57 (dddd, *J* = 5.4, 3.6, 1.9, 1.9 Hz, 1H), 3.37 (ddd, *J* = 4.5, 4.5, 1.0 Hz, 1H), 3.25 (m, 1H), 3.03 (dddd, *J* = 6.7, 4.8, 1.9, 1.9 Hz, 1H), 2.70 (m, 1H), 2.65 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 200.46, 142.12, 137.62, 136.88, 136.81, 133.23, 129.03, 128.91, 128.86, 128.08, 127.51, 96.00, 82.62, 56.33, 55.61, 44.88, 43.50, 42.00, 41.31, 38.30. GCMS *m/z*: 77 (67), 105 (100), 235 (16), 262 (34), 340 (M⁺, 5). HRMS (ESI) calcd for C₂₄H₂₁O₂⁺ (MH⁺) 341.1536, found 341.1531.

2. Preparation of the oxametathesis products (3-7):

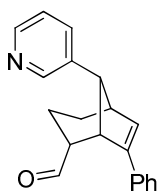
(A) BF₃-catalyzed formation of aldehydes 3: BF₃-Et₂O (small molar excess per heteroatom in **2**) was added to a solution of oxetane **2** in dichloromethane (DCM) and stirred overnight at room temperature, washed twice with a saturated solution of Na₂CO₃ and water. The crude aldehyde **3** was purified on a silica gel column using hexane–ethyl

acetate as an eluent. For pyridine-containing aldehydes hexane–ethanol was used as the eluent.

(B) HCl-catalyzed formation of aldehydes 3: To a solution of **2** in DCM, a catalytic amount of HCl (4.0 M solution in dioxane) was added. The resulting mixture was stirred at room temperature for 24 h, washed twice with a saturated solution of Na₂CO₃ and water, concentrated, and purified on a silica gel column using hexane–ethyl acetate (or hexane–ethanol for the pyridine-containing hemiacetals).

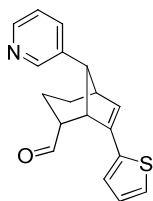
(C) Oxametathesis yielding hemi-acetals 4: To a solution of **2** in DCM, a catalytic amount of HCl (4.0 M solution in dioxane) and 1-3 drops of water were added. The resulting mixture was stirred at room temperature for 24 h, washed twice with a saturated solution of Na₂CO₃ and water, concentrated, and purified on a silica gel column using hexane–ethyl acetate (or hexane–ethanol for the pyridine-containing hemiacetals).

(D) Oxametathesis in alcohols yielding acetals 6: Oxetane **2** was dissolved in a 5% HCl solution in methanol or benzyl alcohol and stirred for 24 h. The resulting mixture was evaporated, dissolved in DCM, washed twice with saturated Na₂CO₃ and water. The crude acetals **6** or **7** were purified on a silica gel column using hexane–ethanol as an eluent.



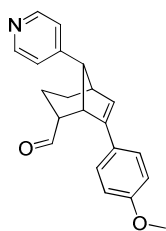
7-Phenyl-syn-8-(3-pyridyl)bicyclo[3.2.1]oct-6-ene-endo-2-carboxaldehyde (3g): (method B) from 0.040 g (0.14 mmol) of **2g** and 100 μ L of HCl (4.0 M, 0.42 mmol) in DCM: 0.029 g (72%). ¹H NMR (400 MHz, CDCl₃) δ = 9.44 (d, *J*

= 1.6 Hz, 1H), 8.64 (m, 1H), 8.52 (d, J = 4.6 Hz, 1H), 7.88 (d, J = 7.3 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 7.7 Hz, 2H), 7.35 (m, 2H), 7.27 (m, 1H), 6.61 (d, J = 3.4 Hz, 1H), 4.01 (d, J = 4.3 Hz, 1H), 3.70 (m, 1H), 3.32 (m, 1H), 2.52 (m, 1H), 1.83-1.72 (m, 2H), 1.55-1.43 (m, 2H). HRMS (ESI) calcd for $C_{20}H_{20}NO^+$ (MH^+) 290.1539, found 290.1533.



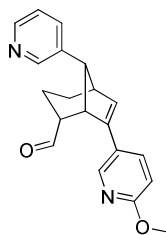
***syn*-8-(3-pyridyl)-7-(2-thienyl)bicyclo[3.2.1]oct-6-ene-endo-2-**

carboxaldehyde (3i): (method B) from 0.150 g (0.51 mmol) of **2i** and 0.25 mL of HCl (4.0 M, 1.02 mmol) in DCM: 0.096 g (64%), as 1.9:1 mixture of epimers (after silica gel column using hexane/EtOH gradient 20:1 to 10:1). 1H NMR (400 MHz, $CDCl_3$) δ = 9.55 (d, J = 1.4 Hz, 1H), 8.93* (s, 1H, epimer), 8.61 (ddd, J = 2.3, 1.2, 1.2 Hz, 1H), 8.52 (m, 1H), 7.64 (dddd, J = 7.9, 2.5, 1.5, 1.5 Hz, 1H), 7.35 (dd, J = 8.0, 4.8 Hz, 1H), 7.20 (m, 1H), 6.98 (m, 1H), 6.95 (d, J = 3.3 Hz, 1H), 6.42 (d, J = 3.4 Hz, 1H), 3.90 (d, J = 4.7 Hz, 1H), 3.69 (t, J = 4.5 Hz, 1H), 3.29 (m, 1H), 2.51 (m, 1H), 1.80-1.70 (m, 2H), 1.55 (m, 1H), 1.45 (m, 1H). HRMS (ESI) calcd for $C_{18}H_{18}NOS^+$ (MH^+) 296.1104, found 296.1106. Sodium ion-bound: HRMS (ESI) calcd for $C_{18}H_{17}NNaOS^+$ (MNa^+) 318.0923, found 318.0913.



7-(4-Methoxyphenyl)-syn-8-(4-pyridyl)bicyclo[3.2.1]oct-6-ene-endo-2-

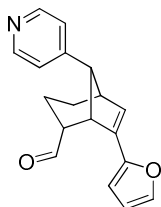
carboxaldehyde (3j): (method B) from 70 mg (0.22 mmol) of **2j** and 28 μ L of HCl (4.0 M, 0.11 mmol) in DCM: 65 mg (93%). ^1H NMR (400 MHz, CDCl_3) δ = 9.42 (d, J = 1.65 Hz, 1H), 8.63 (d, J = 5.9 Hz, 2H), 7.42 (d, J = 8.9 Hz, 2H), 7.27 (d, J = 4.8 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.45 (d, J = 3.3 Hz, 1H), 3.93 (dd, J = 4.7, 1.7 Hz, 1H), 3.82 (s, 3H), 3.61 (t, J = 4.5 Hz, 1H), 3.25 (m, 1H), 2.47 (dddd, J = 11.6, 5.4, 1.8, 1.8 Hz, 1H), 1.77 (dddd, J = 12.5, 12.5, 12.5, 6.5 Hz, 1H), 1.70 (m, J = 12.0, 5.4, 2.1 Hz, 1H), 1.52-1.40 (2H). ^{13}C NMR (400 MHz, CDCl_3) δ = 204.72, 159.55, 150.46, 148.95, 142.79, 127.48, 127.27, 127.00, 123.73, 114.26, 55.48, 52.11, 43.25, 41.61, 39.97, 18.78, 17.77.



7-(4-Methoxy-3-pyridyl)-syn-8-(3-pyridyl)bicyclo[3.2.1]oct-6-ene-endo-

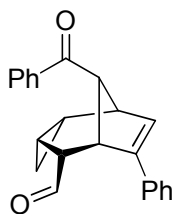
2-carboxaldehyde (3k): (method A) from 0.068 g (0.21 mmol) of **2k** and 0.22 mL of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (48%, 1.75 mmol) in DCM: 0.067 g (98%) (hexane/EtOH gradient 20:1 to 15:1). ^1H NMR (400 MHz, CDCl_3) δ = 9.98 (d, J = 0.9 Hz, 1H), 8.62 (m, 1H), 8.52 (ddd, J = 4.7, 1.3, 1.3 Hz, 1H), 8.28 (d, J = 2.5 Hz, 1H), 7.73 (dd, J = 8.7, 2.5 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.36 (dd, J = 7.9, 4.8 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 6.50 (d, J = 3.4 Hz, 1H), 3.99 (d, J = 4.6 Hz, 1H), 3.95 (s, 3H), 3.69 (t, J = 4.6 Hz, 1H), 3.30 (q, J = 3.7 Hz, 1H), 2.53 (m, 1H), 1.80-1.69 (m, 2H), 1.55 (m, 1H), 1.45 (m, 1H). ^{13}C NMR (400

MHz, CDCl₃) δ = 203.94, 163.87, 150.07, 147.67, 144.67, 140.44, 136.55, 136.05, 134.96, 128.71, 123.99, 111.16, 53.78, 50.66, 42.98, 41.34, 40.15, 18.87, 17.65. HRMS (ESI) calcd for C₂₀H₂₀N₂NaO₂⁺ (MNa⁺) 343.1417, found 343.1401.



***syn*-8-(4-pyridyl)-7-(2-furanyl)bicyclo[3.2.1]oct-6-ene-endo-2-**

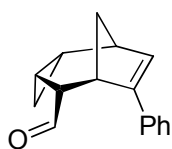
carboxaldehyde (3h): (method C): from 40 mg (0.14 mmol) of **2h** and 72 μ L of HCl (4.0 M, 0.28 mmol) in DCM: trace amount of aldehyde **3h** was obtained after the column chromatography (hemiacetal **4h** was the major product after the column). ¹H NMR (400 MHz, CDCl₃) δ = 9.55 (s, 1H), 9.04* (s, 1H, epimer), 8.63 (d, J = 6.1 Hz, 2H), 7.38 (m, 1H), 7.20 (d, J = 6.1 Hz, 2H), 6.44 (d, J = 3.4 Hz, 1H), 6.40 (dd, J = 3.4, 1.9 Hz, 1H), 6.31 (d, J = 3.3 Hz, 1H), 3.78 (d, J = 4.8 Hz, 1H), 3.62 (m, 1H), 3.26 (m, 1H), 2.47 (m, 1H), 1.76-1.63 (m, 2H), 1.54 (m, 1H), 1.44 (m, 1H). HRMS (ESI) calcd for C₁₈H₁₈NO₂⁺ (MH⁺) 280.1332, found 280.1343.



***syn*-9-Benzoyl-8-phenyltricyclo[4.2.1.0^{3,5}]non-7-ene-endo-2-**

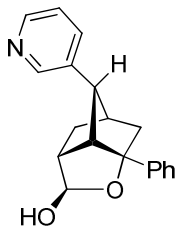
carboxaldehyde (3r): (method A) from 0.17 g (0.52 mmol) of (**2r**) and 0.27 mL of BF₃•Et₂O (48%, 2.17 mmol) in DCM: 0.16 g (94%) (hexane/EtOAc gradient 20:1 to 10:1). ¹H NMR (400 MHz, CDCl₃) δ = 9.92 (s, 1H), 8.00 (d, J = 7.1 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.51 (m, 4H), 7.38 (t, J = 7.7 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 6.18 (d, J =

3.6 Hz, 1H), 3.93 (t, $J = 4.2$ Hz, 1H), 3.63 (d, $J = 4.0$ Hz, 1H) overlaps with 3.61 (ddd, $J = 7.7, 4.1, 4.1$ Hz, 1H), 2.26 (s, 1H), 1.33 (ddd, $J = 9.0, 9.0, 5.6$ Hz, 1H), 0.69 (dddd, $J = 8.3, 8.3, 7.2, 4.9$ Hz, 1H), 0.57 (ddd, $J = 8.8, 8.8, 5.0$ Hz, 1H), 0.39 (q, $J = 5.1$ Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) $\delta = 203.50, 201.17, 147.92, 137.18, 133.33, 133.28, 129.09, 128.91, 128.33, 128.30, 126.93, 125.71, 55.66, 42.49, 42.05, 41.34, 11.48, 7.31, 6.91$.



8-Phenyltricyclo[4.2.1.0^{3,5}]non-7-ene-endo-2-carboxaldehyde (3s):

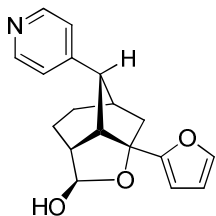
(method B) from 0.17 g (0.76 mmol) of **2s** and 0.27 mL of HCl (4.0 M, 1.10 mmol) in DCM. NMR of reaction mixture showed >90% conversion. However, attempts to purify it on the column failed due to losses and complete epimerization.



1-Phenyl-7-(3-pyridyl)-2-oxatricyclo[4.2.1.0^{4,8}]nonan-3-ol (4b): (method

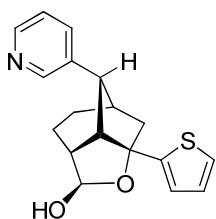
C) from 0.045 g (0.16 mmol) of **2b** and 0.16 mL of HCl (4.0 M, 0.65 mmol) in DCM: 0.031 g (67%) (hexane/EtOH gradient 10:1 to 5:1). ^1H NMR (400 MHz, CDCl_3) $\delta = 8.58$ (m, 1H), 8.48 (d, $J = 4.5$ Hz, 1H), 7.61-7.57 (m, 3H), 7.38 (t, $J = 7.3$ Hz, 2H), 7.31-7.22 (m, 2H), 5.39 (s, 1H), 3.42 (ddd, $J = 4.3, 1.5, 1.5$ Hz, 1H), 3.37 (m, 1H), 2.79 (t, $J = 3.7$ Hz, 1H), 2.69 (exchanges, m, 1H), 2.57 (ddd, $J = 10.8, 4.2, 2.6$ Hz, 1H), 2.33 (ddd, $J = 13.0, 3.3, 3.3$ Hz, 1H), 1.91 (d, $J = 13.1$ Hz, 1H), 1.76 (dddd, $J = 13.3, 10.9, 4.2, 3.0$ Hz, 1H), 1.37 (d, $J = 13.1$ Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) $\delta = 149.35, 147.93, 144.51,$

135.54, 135.23, 128.61, 127.46, 125.72, 123.46, 101.88, 91.14, 54.00, 51.50, 47.40, 45.95, 40.33, 30.22. HRMS (ESI) calcd for $C_{19}H_{20}NNO_2^+$ (MH^+) 294.1489, found 294.1486.



1-(2-Furanyl)-8-(4-pyridyl)-2-oxatricyclo[4.2.1.0^{4,9}]decan-3-ol (4h):

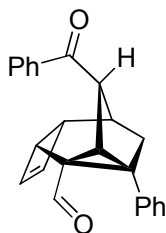
(method C) from 0.040 g (0.14 mmol) of **2h**, 72 μ L of HCl (4.0 M, 0.29 mmol) in dioxane and 72 μ L of water (4.00 mmol) in DCM/dioxane mixture: 0.041 g (97%) w/o chromatography. 1H NMR (400 MHz, $CDCl_3$) δ = 8.54 (d, J = 6.1 Hz, 2H), 7.41 (dd, J = 1.7, 0.9 Hz, 1H), 7.30 (m, 2H), 6.33 (m, 2H), 5.30 (s, 1H), 3.59 (ddd, J = 7.8, 4.9, 1.5 Hz, 1H), 3.24 (t, J = 4.3 Hz, 1H), 2.84 (m, 2H), 2.68 (ddd, J = 8.1, 8.1, 1.7 Hz, 1H), 2.36 (ddd, J = 13.6, 5.8, 1.1 Hz, 1H), 2.05 (d, J = 13.6 Hz, 1H), 1.95 (ddd, J = 14.2, 8.9, 8.9 Hz, 1H), 1.63 (ddd, J = 14.0, 9.7, 9.7 Hz, 1H), 1.22 (m, 1H), 1.11 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 158.07, 151.26, 150.17, 142.43, 122.65, 110.51, 106.43, 105.92, 90.62, 48.59, 46.46, 45.94, 45.11, 34.59, 24.57, 19.29. HRMS (ESI) calcd for $C_{18}H_{20}NO_3^+$ (MH^+) 298.1438, found 298.1430.



8-(3-Pyridyl)-1-(2-thienyl)-2-oxatricyclo[4.2.1.0^{4,9}]decan-3-ol (4i):

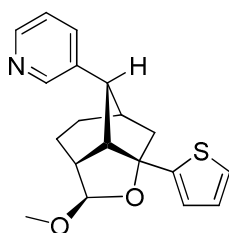
(method C) from 0.071 g (0.24 mmol) of **2i**, 0.30 mL of HCl (4.0 M, 1.20 mmol) and 0.30 mL of water (17 mmol) in benzene/dioxane: 0.07 g (93%) w/o chromatography. 1H

NMR (400 MHz, CDCl₃) δ = 8.67 (m, 1H), 8.49 (d, J = 4.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.27 (dd, J = 7.9, 4.8 Hz, 1H), 7.20 (dd, J = 5.1, 1.2 Hz, 1H), 7.04 (dd, J = 3.6, 1.2 Hz, 1H), 6.97 (dd, J = 5.1, 3.6 Hz, 1H), 5.36 (s, 1H), 3.56 (ddd, J = 7.7, 4.9, 1.6 Hz, 1H), 3.41 (t, J = 4.3 Hz, 1H), 2.91 (m, 1H), 2.80 (s, 1H), 2.69 (ddd, J = 8.1, 8.1, 1.9 Hz, 1H), 2.37 (dd, J = 13.7, 5.7 Hz, 1H), 2.22 (d, J = 13.7 Hz, 1H), 1.95 (ddd, J = 14.1, 9.1, 9.1 Hz, 1H), 1.64 (ddd, J = 14.7, 9.3, 9.3 Hz, 1H), 1.24 (m, 1H), 1.13 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 153.27, 148.85, 147.61, 137.44, 134.75, 127.13, 124.11, 123.70, 122.37, 106.34, 93.29, 52.23, 51.30, 44.94, 44.50, 35.14, 24.39, 19.39. HRMS (ESI) calcd for C₁₈H₁₉NNaO₂S⁺ (MNa⁺) 336.1029, found 336.1027.



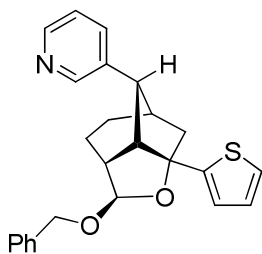
***syn*-10-Benzoyl-9-phenyltertracyclo[5.2.1.0.^{2,9}0^{3,6}]dec-4-ene-2-**

carboxaldehyde (5t): (method B) from 0.065 g (0.20 mmol) of **2t** and 100 μ L of HCl (4.0 M, 0.40 mmol) in DCM: 0.059 g (90%) (hexane/EtOAc gradient 20:1 to 10:1). ¹H NMR (400 MHz, CDCl₃) δ = 8.59 (s, 1H), 8.02 (d, J = 7.1 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.35-7.30 (m, 4H), 7.28-7.23 (m, 1H), 6.50 (d, J = 2.7 Hz, 1H), 5.80 (d, J = 2.7 Hz, 1H), 4.41 (dd, J = 5.6, 3.0 Hz, 1H), 3.45 (d, J = 4.7 Hz, 1H), 2.86 (d, J = 12.5 Hz, 1H), 2.76 (q, J = 5.1 Hz, 1H), 2.67 (m, 2H), 1.98 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 201.52, 199.89, 141.21, 138.97, 137.77, 136.97, 133.48, 129.03, 128.35, 127.46, 52.56, 43.18, 41.34, 38.51, 37.97, 36.93, 36.87, 28.58. HRMS (ESI) calcd for C₂₄H₂₀NaO₂⁺ (MNa⁺) 363.1356, found 363.1363.



3-Methoxy-8-(3-Pyridyl)-1-(2-thienyl)-2-

oxatricyclo[4.2.1.0^{4,9}]decane (6i): (method D) from 0.160 g (0.54 mmol) of **2i** and 0.80 mL of HCl (4.0 M, 3.24 mmol) in methanol: 0.17 g (96%) (hexane/EtOH 15:1). ¹H NMR (400 MHz, CDCl₃) δ = 8.66 (ddd, *J* = 2.3, 1.1, 1.1 Hz, 1H), 8.48 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.25 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.21 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.01 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.81 (s, 1H), 3.50 (ddd, *J* = 7.8, 4.8, 1.6 Hz, 1H), 3.39 (s, 3H), 3.36 (t, *J* = 4.1 Hz, 1H), 2.90 (m, 1H), 2.67 (ddd, *J* = 8.1, 8.1, 1.8 Hz, 1H), 2.38 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.22 (d, *J* = 13.7 Hz, 1H), 1.95 (ddd, *J* = 14.2, 8.8, 8.8 Hz, 1H), 1.65 (dt, *J* = 14.4, 9.4 Hz, 1H), 1.24 (m, 1H), 1.14 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 152.67, 148.83, 147.57, 137.43, 134.64, 126.85, 124.30, 123.63, 122.44, 113.16, 92.89, 55.17, 52.38, 50.91, 44.42, 44.37, 35.04, 24.48, 19.57. HRMS (ESI) calcd for C₁₉H₂₂NO₂S⁺ (MH⁺) 328.1366, found 328.1360.



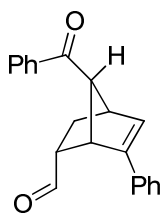
3-Benzyloxy-8-(3-Pyridyl)-1-(2-thienyl)-2-

oxatricyclo[4.2.1.0^{4,9}]decane (7i): (method D) from 0.040 g (0.14 mmol) of **2i** and 0.21 mL of HCl (4.0 M, 0.84 mmol) in benzyl alcohol: 0.041 g, (72%) (hexane/EtOH 20:1). ¹H NMR (400 MHz, CDCl₃) δ = 8.68 (dd, *J* = 2.3, 1.2 Hz, 1H), 8.48 (d, *J* = 4.8 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.32-7.21 (m, 7H), 7.05 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.97 (dd, *J* =

5.1, 3.6 Hz, 1H), 5.01 (s, 1H), 4.80 (d, $J = 11.8$ Hz, 1H), 4.44 (d, $J = 1.8$ Hz, 1H), 3.63 (ddd, $J = 7.7, 4.9, 1.6$ Hz, 1H), 3.38 (t, $J = 4.2$ Hz, 1H), 2.91 (m, 1H), 2.75 (ddd, $J = 8.1, 8.1, 1.8$ Hz, 1H), 2.37 (dd, $J = 13.6, 5.7$ Hz, 1H), 2.25 (d, $J = 13.6$ Hz, 1H), 1.96 (ddd, $J = 14.1, 9.1, 9.1$ Hz, 1H), 1.67 (dt, $J = 14.2, 9.5$ Hz, 1H), 1.22 (m, 1H), 1.13 (m, 1H). ^{13}C NMR (400 MHz, CDCl_3) $\delta = 152.70, 148.87, 147.59, 138.16, 137.49, 134.71, 128.56, 128.28, 127.79, 126.87, 124.30, 123.64, 122.41, 110.97, 92.95, 69.15, 52.21, 51.10, 44.58, 44.45, 35.13, 24.51, 19.56$. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{25}\text{NNaO}_2\text{S}^+$ (MNa^+) 426.1498, found 426.1503.

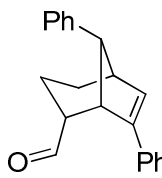
3. Preparation of aldehydes 3 via external irradiation.

Extended irradiation with RPR-3000 caused oxetanes **2** to convert to aldehydes **3**. We believe this is an indirect effect, i.e. that irradiation with shorter wavelengths causes the formation of catalytic amount of HCl, which further accelerates metathesis in cases, where Ar = Ph or Bz. Experimentally, oxetanes cyclorevert much slower in reagent grade DCM in the dark. Irradiation with RPR-3000 accelerates the cycloreversion. It is conceivable that cycloreversion is accelerated via direct excitation of oxetane's aromatic moiety at shorter wavelengths, but it is unlikely: addition of 1% pyridine as proton scavenger does not affect photo cycloaddition but completely inhibits cycloreversion. In this series of experiments the oxetanes were simply irradiated with RPR-3000 for 24 hours in dichloromethane.



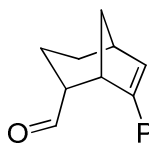
***syn*-7-Benzoyl-6-phenylbicyclo[2.2.1]hept-5-ene-endo-2-carboxaldehyde**

(3a): from 0.05 g (0.165 mmol) of **2a** in 2 mL of DCM: 0.021 g (42%) (hexane/EtOAc gradient 30:1 to 10:1). ^1H NMR (400 MHz, CDCl_3) δ = 9.35 (d, J = 2.6 Hz, 1H), 7.94 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.3 Hz, 2H), 7.25 (d, J = 7.3 Hz, 1H), 6.67 (d, J = 3.4 Hz, 1H), 4.07 (dddd, J = 3.2, 1.6, 1.6, 1.6 Hz, 1H), 3.50 (dt, J = 1.6, 1.6 Hz, 1H), 3.43 (dddd, J = 3.5, 3.5, 1.8, 1.8 Hz, 1H), 3.27 (dddd, J = 8.8, 3.4, 3.4, 3.4 Hz, 1H), 2.07 (ddd, J = 12.5, 8.95, 3.7 Hz, 1H), 1.69 (ddd, J = 12.5, 3.9, 1.7 Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ = 203.94, 198.63, 145.44, 135.94, 134.48, 133.55, 130.66, 129.00, 128.94, 128.83, 128.52, 128.36, 128.13, 125.20, 66.34, 49.89, 47.87, 46.09, 26.03.



***syn*-7,8-Diphenylbicyclo[3.2.1]oct-6-ene-endo-2-carboxaldehyde (3e):**

from 0.058 g (0.20 mmol) of **2e** in 2 mL of DCM: 0.045 g (78%) (hexane/EtOAc gradient 40:1 to 20:1) as a 2.6:1 mixture of epimerized aldehydes. ^1H NMR (400 MHz, CDCl_3) δ = 9.38 (d, J = 1.4 Hz, 1H), 9.10* (s, 1H, epimer), 7.43 (d, J = 7.4 Hz, 2H), 7.36-7.14 (m, 8H), 6.53 (d, J = 3.4 Hz, 1H), 3.93 (d, J = 4.7 Hz, 1H), 3.60 (dd, J = 4.7, 4.7 Hz, 1H), 3.18 (m, 1H), 2.53 (m, 1H), 1.71 (m, J = 12.5, 5.8, 2.1 Hz, 1H), 1.63 (m, 1H), 1.33 (m, 2H). HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{20}\text{NaO}^+$ (MNa^+) 311.1406, found 311.1395.

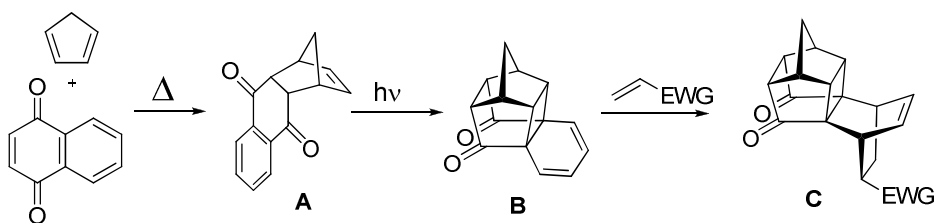


7-Phenylbicyclo[3.2.1]oct-6-ene-endo-2-carboxaldehyde (3f): from 0.046 g (0.217 mmol) of **2f** in 2 mL of DCM: 0.031 g (68%) (hexane/EtOAc gradient 40:1 to 20:1) as a mixture of epimerized aldehydes. ^1H NMR (400 MHz, CDCl_3) δ = 9.38 (d, J = 2.2 Hz, 1H), 9.08* (s, 1H, epimer), 7.41 (d, J = 7.7 Hz, 2H), 7.29 (t, J = 7.4 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 6.36 (d, J = 3.1 Hz, 1H), 3.47 (d, J = 5.4 Hz, 1H), 2.79 (dddd, J = 5.9, 3.0, 3.0, 3.0 Hz, 1H), 2.43 (dddd, J = 11.5, 5.5, 2.3, 2.3 Hz, 1H), 2.34 (ddd, J = 10.3, 5.2, 5.2 Hz, 1H), 1.84 (m, 1H), 1.70 (m, 1H), 1.62 (d, J = 10.2 Hz, 1H), 1.57 (d, J = 9.8 Hz, 1H), overlaps with 1.57 (m, 1H).

Chapter Three: Oxametathesis in the chromone series

A. Introduction.

This chapter describes our efforts to further explore new dienes, which we employed to dramatically increase the complexity of new polycyclic oxetanes. The *D.-A.* adducts of 1,4-naphthoquinone with cyclic dienes are known to undergo photoinduced [2+2] cycloaddition **A** \rightarrow **B**, disrupting the aromatic system and producing a cyclohexadiene moiety [32]. Coxon, Marchand and co-workers studied facial selectivity in the *D.-A.* reactions of **B**, which primarily produced compound **C** as a result of an attack by a dienophile at the face containing the carbonyl groups [33]:



It was rather unexpected to realize that 1,4-naphthoquinones are the only aromatic ketones that are reported to form polycyclic dienes of type **B** in intramolecular [2+2] photo-cycloadditions.

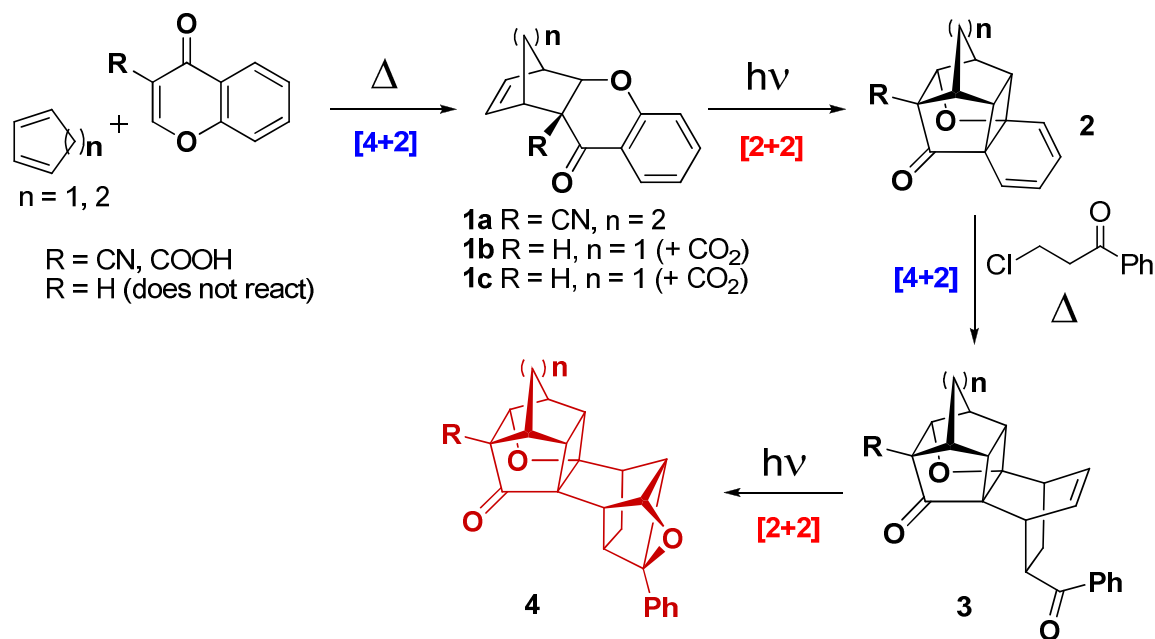
Very few benzo-fused aromatic ketones have been reported as good dienophiles for the first, i.e. *D.-A.* step (\rightarrow **A**). For example, chromones had received very little attention, until Hsung reported the first stereoselective [4+2] cycloaddition reactions of 3-

cyanochromone derivatives with electron-rich dienes [34]. We hypothesized that this or similar re-generated diene can be used instead of simple cyclopentadiene or cyclohexadiene.

B. Results and discussion.

This chapter describes another high-yielding photoprotolytic transformation. Herein we developed a tandem ground state – excited state $[4_{\pi}+2_{\pi}]^{\circ}[2_{\pi}+2_{\pi}]$ sequence, where the second photochemical *Paternò-Büchi* (*P.-B.*) step in a strained polycyclic molecular framework is accompanied by an acid-catalyzed fragmentation.

Our basis for the present study was (a) to estimate the feasibility of the intramolecular $[2+2]$ photoinduced cycloaddition in the *D.-A.* adducts of chromone derivatives, and (b) to determine whether secondary *D.-A.* addition, the *P.-B.* step and the following “one-pot” protolytic oxametathesis is possible (Scheme 25):



Scheme 25. A tandem ground state – excited state $[4_{\pi}+2_{\pi}]^{\circ}[2_{\pi}+2_{\pi}]$ sequence [35].

Our first attempts were unsuccessful, since in the first *D.-A.* step unsubstituted chromone was not reactive. Only one example of a similar reaction was reported by Richard Hsung in 1997 using 3-cyanochromone [34]. The 3-cyano-group certainly makes the chromone a much more reactive dienophile. While the unsubstituted chromone is not reactive, we found that its “formal” *D.-A.* adducts with cyclic dienes can still be obtained in moderate to good yields of 55-70% via the reactions of chromone-3-carboxylic acid, because the immediate products of this cycloaddition, β -keto acids, undergo thermal decarboxylation into **1b,c** (Scheme 25).

D.-A. adducts **1** undergo clean and quantitative photocyclization into dienes **2** upon irradiation in a Rayonet photoreactor (Figure 11A) with RPR-3500 lamps (a broadband UV source with $\lambda = 350 \pm 50$ nm) or a UVLED-based illuminator with five 250 mW @ 365 nm Nichia chips (Figure 11B). This is the first example of the tandem *D.-A.* reaction followed by an aryl-alkene $[2_{\pi}+2_{\pi}]$ photocyclization involving an aromatic ketone other than a 1,4-naphthoquinone.

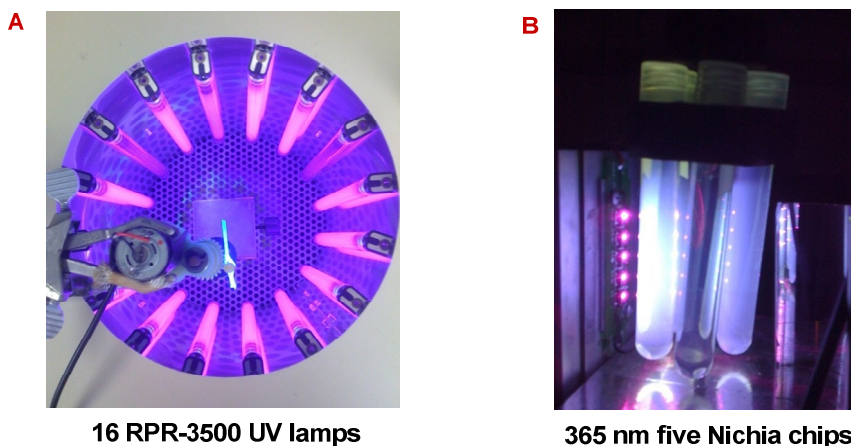
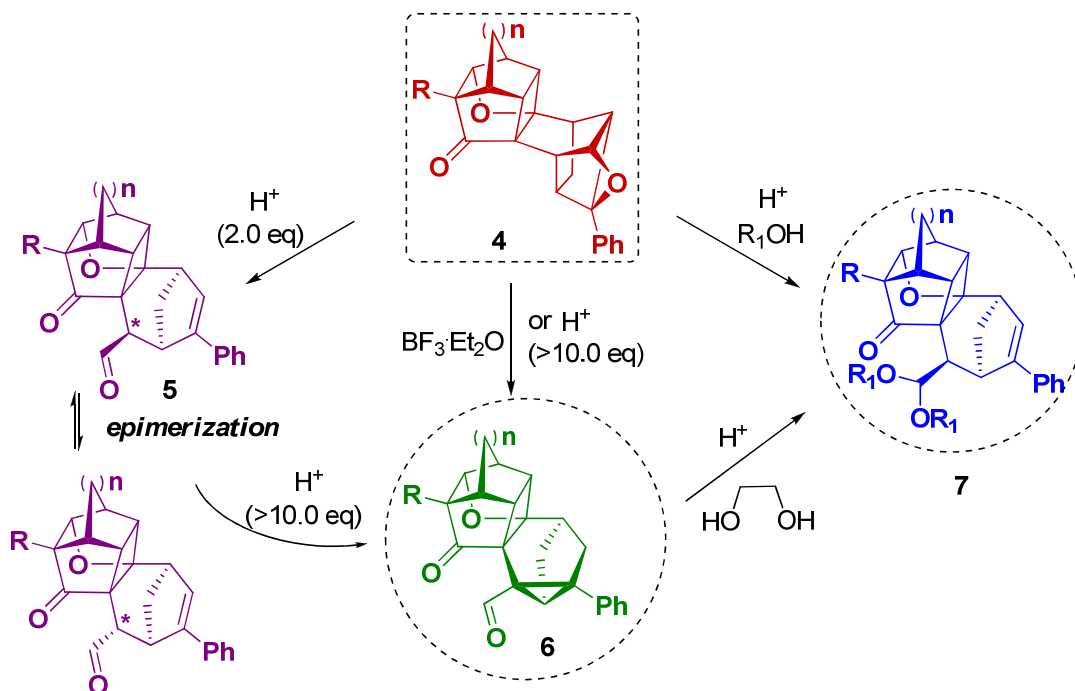


Figure 11. (A) A Rayonet photoreactor with RPR-3500 lamps; (B) a UVLED-based illuminator with five 250 mW @ 365 nm Nichia chips.

Dienes **2** react with dienophiles such as vinyl phenyl ketone, generated *in situ*, to give *D.-A.* adducts **3**. The facial selectivity of this second *Diels-Alder* step is the same as 1,4-naphthoquinone adducts, i.e. the dienophile is approaching from the "ketone" face.

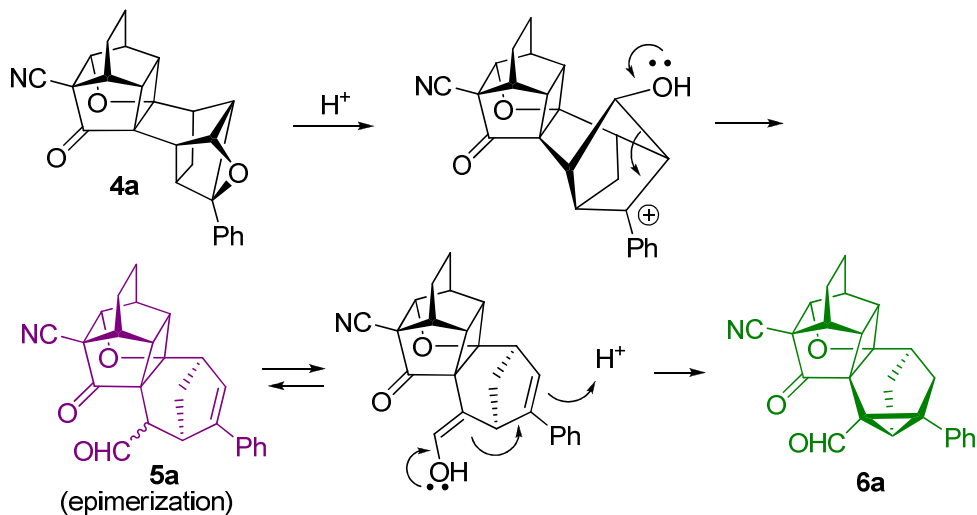
The culmination of this chain of reactions is the *P.-B.* step, leading to quantitative formation of structurally unique oxetanes **4** outfitted with various functional groups. This step is the most critical part of the synthesis, where the strain is captured into the polycyclic scaffold. Such congested systems in the presence of HCl undergo cycloreversion to an alternative alkene-carbonyl pair **5**, which we refer to as an alkene-carbonyl *oxametathesis* [30, 35] (Scheme 26):



Scheme 26. An alkene-carbonyl oxametathesis in chromone series [35].

At first, in the presence of a catalytic amount of HCl-dioxane (4.0 M) in dichloromethane, we observed that oxetanes **4** undergo cycloreversion forming aldehydes **5** in nearly quantitative yields. Further acidolysis of initially produced aldehydes **5** caused

their epimerization and rearrangement yielding aldehydes **6** containing a cyclopropyl ring (Scheme 26 and Scheme 27):



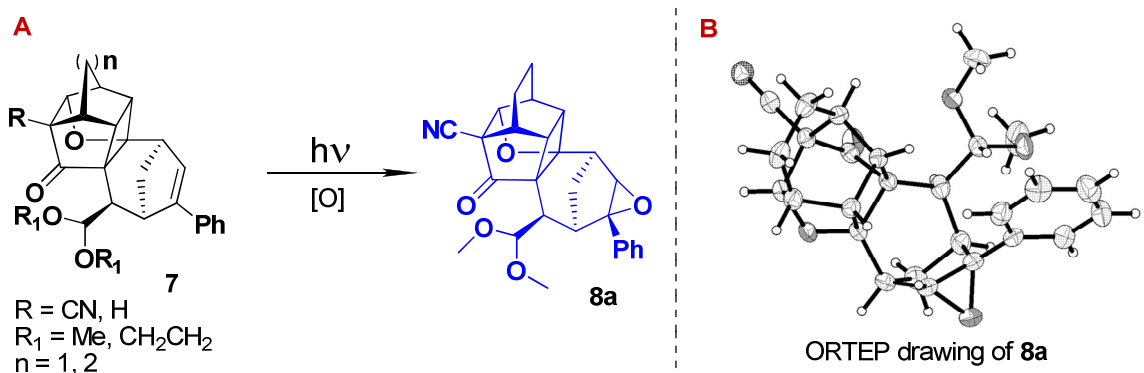
Scheme 27. Photoprotolytic oxametathesis of oxetane **4a** leading to the initial formation of a mixture of epimers **5a** following by formylcyclopropane **6a**.

We believe that products **6** (analogous to **5t** described in chapter two) can be formed as a result of a secondary electrophilic attack of H^+ on the newly formed styrene moiety followed by nucleophilic participation of the intermediate enol (Scheme 27). To avoid the formation of complicated mixtures, this reaction can be carried out in the presence of a strong Lewis acid, like $BF_3 \cdot Et_2O$, or a large excess of HCl. In those cases we observed exclusively the formation of formylcyclopropanes **6**.

When the cycloreversion is carried out in alcohols as solvents, acetals of type **7** are formed in high yields (Scheme 26). We observed that the formation of formylcyclopropanes **6** is reversible and products **7** could also be obtained from aldehydes **6**, which were treated with HCl in the presence of methanol and ethylene glycol.

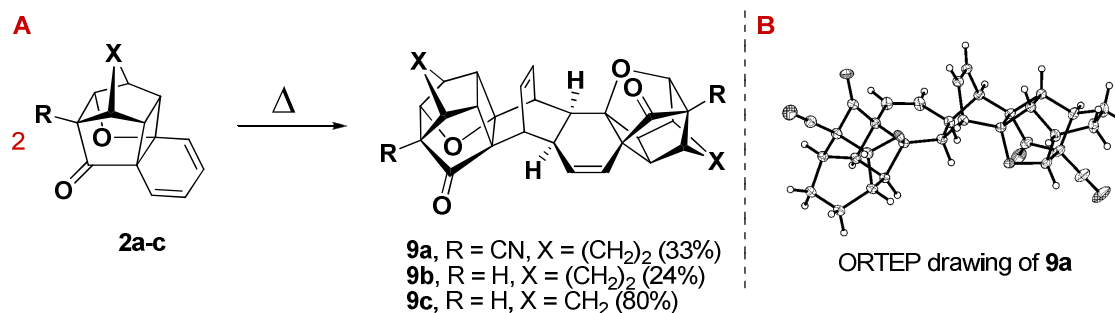
It is worth mentioning that the regio- and stereochemical outcome of the overall synthetic sequence from chromones **1** to products **5**, **6** and **7** is not decided at the photoprotolytic oxametathesis step. The configuration inherent in **3** is simply passed on to rearranged products **5**, **6** and **7**.

At this point two remarkable reactions that we discovered unexpectedly should be mentioned. In the first case we observed that irradiation of some acetals **7** resulted in formation of pure compounds, which were missing double bonds. X-ray diffraction confirmed that an oxirane ring was forming (Scheme 28). This prominent photo-epoxidation example provides another opportunity to increase functional diversity. The exact mechanism remains unknown [54]. It is unclear whether this reaction occurs through the formation of a peroxyepoxide or through photosensitization, but the products are formed in high yields (> 85 % by NMR).



Scheme 28. (A) Photo-epoxidation example of acetal **7a**; (B) the ORTEP drawing of X-ray structure of **8a**.

Another striking observation was that the chromone-based polycyclic dienes **2**, while being heated in a pressure vessel, underwent the *D.-A.* cyclodimerization yielding a single diastereomeric product **9** containing 20 stereocenters (Scheme 29).



Scheme 29. (A) The *D*-*A*. dimerization of **2a-c**; (B) the ORTEP drawing of the X-Ray structure of **9a**.

This is an opportunity to create topological diversity. The framework is unique and cannot be synthesized using other simple synthetic methods.

Unlike adducts **2**, 1,4-naphthoquinone-based caged diene **B** (page 57) was reluctant to undergo the dimerization. The comparative electronic population analysis in **B** and **2a** is relevant to this failure of **B** to dimerize. Figure 12 shows that atoms in the diene fragment of **B** are depleted of electronic density to a much greater extent (the cumulative positive charge of the moiety is 1.16 vs 0.405 in **2a**). The electronic density in **2a** is much less depleted and it is also appropriately polarized with the "dienophile" double bond being more electrophilic [35].

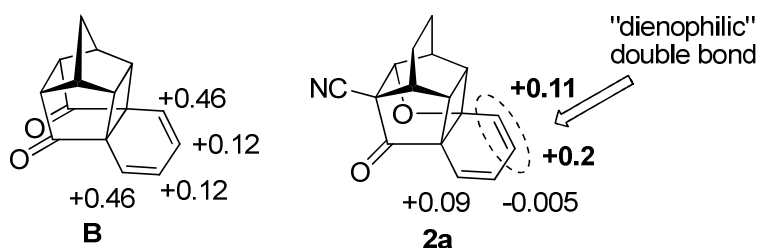


Figure 12. Calculated charges in the diene fragment of **B** and **2a** [35].

In conclusion, we have confirmed that the *Diels-Alder* adducts of chromones are capable of photoinduced alkene-arene [2+2] cycloaddition producing different dienes, which can dimerize or can be introduced into a double-tandem $[4_{\pi}+2_{\pi}]^{\circ}[2_{\pi}+2_{\pi}]^{\circ}[4_{\pi}+2_{\pi}]^{\circ}[2_{\pi}+2_{\pi}]$ synthetic sequence, followed by an acid-catalyzed oxametathesis, leading to expeditious growth of molecular complexity over a few experimentally simple steps. The appealing feature of this approach is that the first *D.-A.* step controls the stereochemical outcome of the entire sequence [35].

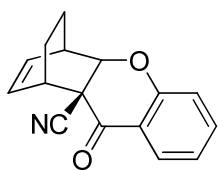
C. Experimental section.

Common solvents were purchased from Pharmco and used as is, except for THF, which was refluxed over and distilled from potassium benzophenone ketyl prior to use. Common reagents were purchased from Aldrich or TCI America and used without additional purification unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz or Varian Mercury 400 MHz instrument in CDCl₃ with TMS as an internal standard (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument (see Appendix B). High resolution mass spectra were obtained on the *MDS SCIEX/Applied Biosystems API QSTARTM Pulsar i Hybrid LC/MS/MS System* mass spectrometer by Dr. Shuji Kato from the University of Colorado at Boulder.

1. Preparation of the *Diels-Alder* adducts (1):

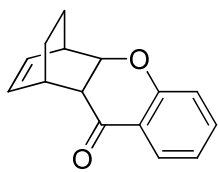
A solution of chromone (1.0 eq) and 1,3-cyclohexadiene (or freshly distilled 1,3-cyclopentadiene) (5.0 eq) in 15 mL of 1,2-dichlorobenzene was heated in a bomb at 200-210°C (for 1,3-cyclohexadiene) and 130-140°C (for 1,3-cyclopentadiene) overnight.

After the reaction was cooled to room temperature, the solvent was removed on a high vacuum pump. The crude reaction mixture was purified on a silica gel column using a mixture of hexane and EtOAc as an eluent. All the X-ray structures can be found in Appendix B.



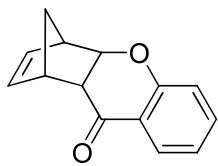
endo-**4,5-Benzo-7-cyano-3-oxatricyclo[6.2.2.0^{2,7}]dodec-9-ene-6-one**

(1a): from 2.50 g of 3-cyanochromone (14.6 mmol) and 7.0 mL of 1,3-cyclohexadiene (73.0 mmol) at 200^oC (hexane/EtOAc gradient 20:1→5:1): 2.19 g (60%). ¹H NMR (500 MHz, CDCl₃) δ = 7.69 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.45 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.80 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.26 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.14 (t, *J* = 7.3 Hz, 1H), 5.06 (ddd, *J* = 7.9, 6.4, 1.2 Hz, 1H), 3.50 (d, *J* = 2.8 Hz, 1H), 3.12 (m, 1H), 2.15 (m, 1H), 1.75 (m, 1H), 1.38 (m, 2H). ¹³C NMR (400 MHz, CDCl₃) δ = 184.35, 159.82, 137.71, 133.64, 132.14, 127.58, 121.89, 120.07, 118.34, 118.08, 82.88, 50.44, 39.73, 37.08, 21.25, 21.08. *exo*-**4,5-benzo-7-cyano-3-oxatricyclo[6.2.2.0^{2,7}]dodec-9-ene-6-one**: (< 3%). ¹H NMR (500 MHz, CDCl₃) δ = 7.85 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.55 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 1H), 7.03 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 6.95 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.58 (m, *J* = 8.5, 5.9 Hz, 1H), 6.48 (ddd, *J* = 8.0, 6.9, 1.4 Hz, 1H), 4.77 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.47 (m, 1H), 3.12 (m, 1H), 1.71-1.65 (m, *J* = 12.8, 9.7, 4.1, 2.5 Hz, 1H), 1.46-1.40 (m, 1H), 1.28-1.22 (m, 1H), 1.20-1.13 (m, 1H).



endo-**4,5-Benzo-3-oxatricyclo[6.2.2.0^{2,7}]dodec-9-ene-6-one (1b)**: from

2.00 g of chromone-3-carboxylic acid (10.5 mmol) and 5.0 mL of 1,3-cyclohexadiene (52.5 mmol) at 200°C (hexane/EtOAc gradient 30:1→10:1): 1.67 g (70%). ¹H NMR (500 MHz, CDCl₃) δ = 7.68 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.36 (ddd, *J* = 8.4, 7.1, 1.8 Hz, 1H), 6.95 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.91 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.28 (ddd, *J* = 8.0, 6.5, 1.3 Hz, 1H), 6.20 (t, *J* = 7.2 Hz, 1H), 4.95 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.27 (m, 1H), 3.12 (m, 1H), 2.86 (dd, *J* = 9.4, 2.1 Hz, 1H), 1.62 (dddd, *J* = 12.3, 9.5, 3.0, 3.0 Hz, 1H), 1.54 (dddd, *J* = 12.5, 9.8, 4.6, 1.8 Hz, 1H), 1.37 (dddd, *J* = 12.1, 12.1, 3.6, 3.6 Hz, 1H), 1.27 (dddd, *J* = 11.8, 11.8, 4.4, 2.8 Hz, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 192.92, 160.95, 136.32, 134.25, 132.27, 126.81, 120.85, 119.73, 117.75, 79.59, 50.73, 36.88, 34.48, 25.54, 20.53. *exo*-**4,5-benzo-3-oxatricyclo[6.2.2.0^{2,7}]dodec-9-ene-6-one**: 0.67 g (28%). ¹H NMR (500 MHz, CDCl₃) δ = 7.81 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.46 (ddd, *J* = 8.3, 7.1, 1.8 Hz, 1H), 6.95 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.91 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.49 (m, *J* = 8.4, 6.2 Hz, 1H), 6.28 (m, *J* = 8.1, 6.8, 1.2 Hz, 1H), 4.64 (ddd, *J* = 11.0, 3.7, 1.1 Hz, 1H), 3.23 (m, 1H), 3.02 (m, 1H), 2.59 (ddd, *J* = 11.0, 2.8, 1.8 Hz, 1H), 1.92 (m, 1H), 1.48 (m, 1H), 1.17 (m, 2H).



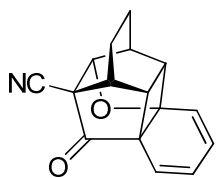
endo-**4,5-Benzo-3-oxatricyclo[6.2.1.0^{2,7}]undec-9-ene-6-one (1c)**: from

2.00 g of chromone-3-carboxylic acid (10.5 mmol) and 3.0 mL of 1,3-cyclopentadiene (36.8 mmol) at 135°C (hexane/EtOAc gradient 60:1→30:1): 1.23 g (55%). ¹H NMR (500

MHz, CDCl₃) δ = 7.69 (dd, J = 7.9, 1.7 Hz, 1H), 7.36 (ddd, J = 8.4, 7.1, 1.8 Hz, 1H), 6.85 (ddd, J = 8.0, 7.2, 1.0 Hz, 1H), 6.74 (dd, J = 8.4, 1.0 Hz, 1H), 6.11 (m, 2H), 5.25 (dd, J = 9.3, 4.0 Hz, 1H), 3.49 (m, 2H), 3.14 (dd, J = 9.2, 3.9 Hz, 1H), 1.46 (ddd, J = 9.2, 1.9, 1.9 Hz, 1H), 1.36 (d, J = 9.2 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 193.41, 160.96, 137.20, 136.53, 134.53, 126.63, 120.56, 119.52, 117.67, 79.98, 49.94, 49.34, 48.98, 45.18. ***exo*-4,5-benzo-3-oxatricyclo[6.2.1.0^{2,7}]undec-9-ene-6-one**: 0.56 g (25%). ¹H NMR (500 MHz, CDCl₃) δ = 7.78 (dd, J = 7.9, 1.7 Hz, 1H), 7.42 (ddd, J = 8.6, 7.1, 1.7 Hz, 1H), 6.92 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 6.88 (dd, J = 8.4, 1.0 Hz, 1H), 6.44 (dd, J = 5.7, 3.0 Hz, 1H), 6.10 (dd, J = 5.7, 3.2 Hz, 1H), 4.61 (ddd, J = 8.0, 1.3, 1.3 Hz, 1H), 3.36 (m, 1H), 3.27 (m, 1H), 2.58 (dd, J = 8.0, 1.8 Hz, 1H), 1.67 (d, J = 9.4 Hz, 1H), 1.55 (m, J = 9.4, 1.6 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 192.86, 160.90, 141.78, 136.55, 133.82, 127.12, 120.99, 120.08, 118.08, 80.10, 51.72, 48.44, 48.37, 45.28.

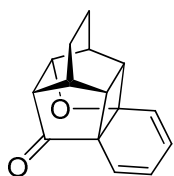
2. Preparation of the [2+2] adducts (2):

An approximately 10 mM solution of an *endo*-precursor **1** in benzene (or other specified solvents) was irradiated in Pyrex or glass reaction vessels in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) for 24-48 hours. Irradiation resulted in a quantitative conversion to **2**, which were used without further purification (unless purification was required).



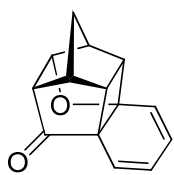
15-Cyano-13-oxahexacyclo[6.4.4.0.0^{2,7}.0^{3,14}.0^{6,15}]hexadec-9,11-diene-16-one (2a): from 2.23 g of **1a** (8.9 mmol) in 1.0 L of benzene, irradiation for 24 hrs

(hexane/EtOAc gradient 15:1→5:1): 1.23 g (55%). ^1H NMR (400 MHz, CDCl_3) δ = 6.00 (dd, J = 9.6, 5.8 Hz, 1H), 5.95 (ddd, J = 9.8, 5.8, 1.0 Hz, 1H), 5.54 (d, J = 9.6 Hz, 1H), 5.45 (d, J = 9.8 Hz, 1H), 4.75 (d, J = 4.2 Hz, 1H), 3.43 (ddd, J = 8.0, 5.6, 1.4 Hz, 1H), 2.86 (dd, J = 8.3, 5.0 Hz, 1H), 2.30 (m, 1H), 2.24 (m, 1H), 2.00-1.91 (m, 3H), 1.60-1.54 (m, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ = 199.51, 126.26, 125.70, 121.68, 120.50, 117.25, 84.04, 81.97, 56.43, 53.31, 50.74, 43.04, 36.47, 36.03, 15.82, 14.19.



13-Oxahexacyclo[6.4.4.0.0^{2,7}.0^{3,14}.0^{6,15}]hexadec-9,11-diene-16-one (2b):

from 1.50 g of **1b** (6.6 mmol) in 1.0 L of benzene, irradiation for 24 hrs (hexane/EtOAc gradient 20:1→10:1): 1.05 g (70%). ^1H NMR (500 MHz, CDCl_3) δ = 5.95-5.88 (m, 2H), 5.53 (d, J = 9.4 Hz, 1H), 5.42 (d, J = 9.7 Hz, 1H), 4.60 (dd, J = 8.0, 4.2 Hz, 1H), 3.38 (ddd, J = 7.8, 5.6, 1.5 Hz, 1H), 2.78 (ddd, J = 8.1, 4.8, 2.2 Hz, 1H), 2.73 (ddd, J = 8.1, 3.4, 2.4 Hz, 1H), 2.09 (m, 1H), 1.94 (m, 1H), 1.92-1.86 (m, 1H), 1.82-1.75 (m, 1H), 1.73-1.66 (m, 1H), 1.52-1.45 (dddd, J = 14.0, 11.8, 5.7, 2.5 Hz, 1H). ^{13}C NMR (500 MHz, CDCl_3) δ = 210.10, 125.83, 124.82, 122.58, 122.27, 83.29, 78.73, 57.42, 52.74, 52.30, 45.11, 36.14, 31.31, 17.69, 15.24.



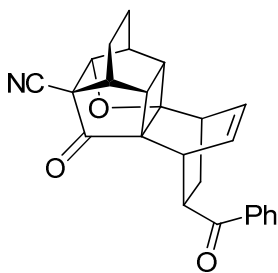
12-Oxahexacyclo[5.4.4.0.0^{2,6}.0^{3,13}.0^{5,14}]pentadec-8,10-diene-15-one (2c):

from 0.89 g of **1c** (4.2 mmol) in 1.0 L of benzene, irradiation for 24 hrs: 0.88 g (> 90%). ^1H NMR (500 MHz, CDCl_3) δ = 6.00 (dd, J = 9.5, 5.7 Hz, 1H), 5.95 (ddd, J = 9.9, 5.7, 1.0 Hz, 1H), 5.63 (d, J = 9.5 Hz, 1H), 5.49 (d, J = 9.9 Hz, 1H), 5.02 (dd, J = 8.4, 4.0 Hz,

1H), 3.42 (ddd, $J = 7.8, 6.0, 1.3$ Hz, 1H), 2.91 (m, 1H), 2.82 (ddd, $J = 8.0, 5.4, 1.9$ Hz, 1H), 2.75 (m, 1H), 2.61 (ddd, $J = 8.4, 4.3, 1.9$ Hz, 1H), 1.80 (d, $J = 11.3$ Hz, 1H), 1.51 (d, $J = 11.5$ Hz, 1H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 211.52, 125.38, 124.62, 122.28, 122.28, 87.05, 83.06, 56.87, 56.29, 55.03, 48.44, 46.25, 42.57, 33.80$.

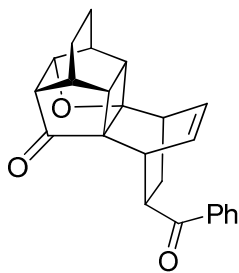
3. Preparation of the *Diels-Alder* adducts (3):

A solution of **2** (1.0 eq) and 3-chloropropiophenone (1.3 eq) in the mixture of 10 mL of pyridine was heated in a bomb at 130-140°C overnight. After the reaction was cooled to room temperature, the solvent was removed on a high vacuum pump. The crude reaction mixture was purified on a silica gel flash column using a mixture of hexane and EtOAc (or EtOH) as an eluent. NOTE: We attempted to further purify reaction mixtures by chromatography. The *Diels-Alder* adducts are not stable on silica gel and *endo*-adducts rearrange into various *exo*-derivatives (*16R(S)*→*16S(R)*) due to the presence of H^+ . To avoid this complication we passed 2 mL of pyridine through the column before filtration.

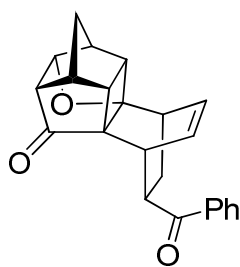


1R(S), 2S(R), 11S(R), 12R(S), 16R(S)-**16-Benzoyl-9-cyano-3-oxaheptacyclo[10.2.2.1^{2,5}.1^{8,11}.0^{2,11}.0^{4,9}.0^{17,18}]octadec-13-ene-10-one (3a)**: from 1.13 g of **2a** (4.5 mmol) and 1.00 g of 3-chloropropiophenone (5.9 mmol) at 140°C (hexane/EtOAc gradient 20:1→1:1): 0.86 g (50%). ^1H NMR (400 MHz, CDCl_3) $\delta = 8.06$ (m, 2H), 7.54 (t, $J = 7.3$ Hz, 1H), 7.45 (m, 2H), 6.39 (ddd, $J = 8.3, 7.2, 1.3$ Hz, 1H), 6.19

(dd, $J = 8.3, 6.3$ Hz, 1H), 4.80 (d, $J = 4.0$ Hz, 1H), 4.43 (ddd, $J = 9.6, 4.8, 2.1$ Hz, 1H), 3.13 (ddd, $J = 6.4, 1.8, 1.8$ Hz, 1H), 2.83 (m, 1H), 2.68 (ddd, $J = 7.4, 5.8, 1.5$ Hz, 1H), 2.3 (m, 1H), 2.16 (m, 1H), 2.11 (dd, $J = 7.6, 5.0$ Hz, 1H), 2.04-1.94 (m, 1H), 1.93-1.85 (m, 4H), 1.54-1.46 (m, 1H). ^{13}C NMR (400 MHz, CDCl_3) $\delta = 203.20, 200.49, 147.47, 136.13, 133.39, 133.21, 131.37, 128.99, 128.94, 117.32, 91.34, 83.36, 57.80, 52.61, 40.17, 36.57, 35.43, 35.09, 33.84, 33.77, 21.93, 16.18, 14.28$. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{21}\text{NNaO}_3^+$ (MNa^+) 406.1414, found 406.1425.



1R(S), 2S(R), 11S(R), 12R(S), 16R(S)-**16-Benzoyl-3-oxaheptacyclo[10.2.2.1^{2,5}.1^{8,11}.0^{2,11}.0^{4,9}.0^{17,18}]octadec-13-ene-10-one (3b)**: from 2.24 g of **2b** (9.9 mmol) and 2.16 g of 3-chloropropiophenone (12.8 mmol) at 140°C (hexane/EtOAc gradient 20:1→10:1): 1.24 g (35%). ^1H NMR (500 MHz, CDCl_3) $\delta = 8.11$ (m, 2H), 7.51 (t, $J = 7.3$ Hz, 1H), 7.44 (m, 2H), 6.37 (ddd, $J = 8.3, 7.2, 1.2$ Hz, 1H), 6.17 (dd, $J = 8.5, 6.1$ Hz, 1H), 4.65 (ddd, $J = 7.7, 4.2, 1.5$ Hz, 1H), 4.50 (ddd, $J = 9.7, 4.8, 2.1$ Hz, 1H), 3.05 (ddd, $J = 6.4, 1.7, 1.7$ Hz, 1H), 2.78 (m, 1H), 2.62-2.57 (m, 2H), 2.02 (m, 1H), 2.01-1.96 (m, 2H), 1.93 (m, 1H), 1.87 (ddd, $J = 12.9, 4.8, 3.2$ Hz, 1H), 1.84-1.79 (m, 1H), 1.77-1.70 (m, 1H), 1.69-1.63 (m, 1H), 1.44-1.38 (m, 1H). ^{13}C NMR (400 MHz, CDCl_3) $\delta = 213.80, 201.26, 136.41, 133.19, 132.93, 131.51, 129.08, 128.80, 90.22, 79.93, 58.14, 52.06, 41.26, 40.37, 35.80, 35.25, 35.06, 34.03, 31.20, 22.17, 18.10, 15.31$. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{O}_3^+$ (MH^+) 359.1642, found 359.1657.



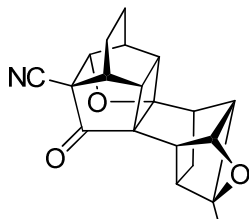
1R(S), 2S(R), 10S(R), 11R(S), 15R(S)-**15-Benzoyl-3-**

oxaheptacyclo[9.2.2.1^{2,5}.1^{7,10}.0^{2,10}.0^{4,8}.0^{16,17}]heptadec-12-ene-9-one (3c): from 0.92 g of **2c** (4.3 mmol) and 0.95 g of 3-chloropropiophenone (5.6 mmol) at 140°C (hexane/EtOAc gradient 20:1→10:1): 0.54 g (36%). ¹H NMR (500 MHz, CDCl₃) δ = 8.12 (m, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.44 (m, 2H), 6.37 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 6.16 (dd, *J* = 8.5, 6.1 Hz, 1H), 5.10 (ddd, *J* = 8.0, 3.7, 1.6 Hz, 1H), 4.46 (ddd, *J* = 9.6, 4.9, 2.2 Hz, 1H), 3.10 (ddd, *J* = 6.4, 1.8, 1.8 Hz, 1H), 2.81 (m, 1H), 2.79-2.74 (m, 2H), 2.63 (m, 1H), 2.50 (ddd, *J* = 8.0, 4.3, 1.9 Hz, 1H), 2.13 (m, 1H), 1.96 (ddd, *J* = 12.7, 9.7, 2.4 Hz, 1H), 1.88 (ddd, *J* = 12.8, 4.9, 3.2 Hz, 1H), 1.79 (d, *J* = 11.4 Hz, 1H), 1.56 (d, *J* = 11.4 Hz, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 214.58, 201.28, 136.41, 133.37, 132.95, 131.60, 129.10, 128.79, 90.61, 88.10, 57.18, 54.25, 47.88, 47.17, 42.11, 40.34, 38.23, 36.34, 35.93, 34.16, 22.45. HRMS (ESI) calcd for C₂₃H₂₁O₃⁺ (MH⁺) 345.1485, found 345.1479.

4. Preparation of the *Paternò-Büchi* adducts (**4**):

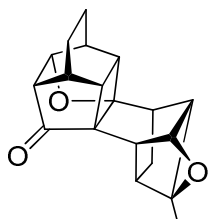
Approximately 1-3 mM solution of a precursor **3** in benzene was irradiated in Pyrex or glass reaction vessels in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) for 48-72 hours. Irradiation resulted in a quantitative conversion to **4**, which were used without further purification. NOTE: We attempted to further purify reaction mixtures by

chromatography. The strained polycyclic oxetanes **4** are not stable on silica gel, producing various amounts of aldehydes **5** via oxametathesis.



Ph 9-Cyano-15-phenyl-3,14-

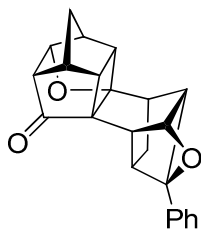
dioxanonacyclo[10.4.2.1^{2,5}.1^{8,11}.0^{2,11}.0^{4,9}.0^{13,16}.0^{15,18}.0^{19,20}]jicosa-10-one (4a): from 1.50 g of **3a** (3.9 mmol) in 1.5 L of benzene, irradiation for 72 hrs: (> 85%). ¹H NMR (500 MHz, CDCl₃) δ = 7.38-7.36 (m, 4H), overlaps 7.36-7.32 (m, 1H), 4.80 (m, 1H), 4.72 (d, *J* = 4.0 Hz, 1H), 3.50 (dddd, *J* = 5.5, 3.5, 1.7, 1.7 Hz, 1H), 2.95-2.91 (m, 2H), 2.74 (ddd, *J* = 6.5, 1.8, 1.8 Hz, 1H), 2.54 (dd, *J* = 7.6, 5.2 Hz, 1H), 2.36 (m, 1H), 2.26 (m, 1H), 2.12 (ddd, *J* = 6.2, 6.2, 1.3 Hz, 1H), 2.01-1.90 (m, 4H), 1.81 (ddd, *J* = 13.2, 6.7, 1.9 Hz, 1H), 1.63-1.56 (m, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 202.03, 136.31, 129.11, 128.75, 127.15, 117.46, 101.10, 90.43, 81.47, 81.37, 56.84, 54.57, 53.16, 44.23, 39.63, 38.59, 37.05, 36.12, 35.43, 32.27, 31.92, 15.92, 14.11. HRMS (ESI) calcd for C₂₅H₂₂NO₃⁺ (MH⁺) 384.1594, found 384.1586.



Ph 15-Phenyl-3,14-

dioxanonacyclo[10.4.2.1^{2,5}.1^{8,11}.0^{2,11}.0^{4,9}.0^{13,16}.0^{15,18}.0^{19,20}]jicosa-10-one (4b): from 1.20 g of **3b** (3.3 mmol) in 1.5 L of benzene, irradiation for 72 hrs: (> 85%). ¹H NMR (500 MHz, CDCl₃) δ = 7.40-7.35 (m, 4H), overlaps 7.35-7.31 (m, 1H), 4.82 (m, 1H), 4.57 (dd,

$J = 8.0, 4.1$ Hz, 1H), 3.49 (dddd, $J = 5.5, 3.6, 1.8, 1.8$ Hz, 1H), 2.91 (d, $J = 6.4$ Hz, 1H), 2.86 (m, $J = 7.6, 5.6, 1.2$ Hz, 1H), 2.69 (ddd, $J = 6.5, 1.8, 1.8$ Hz, 1H), 2.63 (ddd, $J = 8.0, 3.3, 2.4$ Hz, 1H), 2.42 (ddd, $J = 7.5, 5.1, 2.3$ Hz, 1H), 2.12 (m, 1H), 2.08 (m, $J = 6.2, 1.3$ Hz, 1H), 2.03-2.00 (m, 1H), 1.99 (m, 1H), 1.86-1.68 (m, 4H), 1.51 (m, 1H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 213.30, 136.74, 128.89, 128.65, 127.18, 101.17, 89.48, 82.08, 77.94, 57.63, 54.81, 52.45, 44.39, 40.63, 38.67, 37.15, 35.70, 33.52, 32.06, 31.03, 17.78, 15.09$. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{O}_3^+$ (MH^+) 359.1642, found 359.1629.



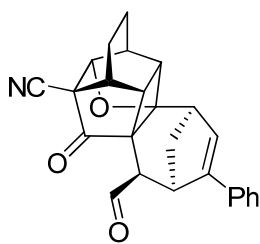
14-Phenyl-3,13-dioxanonacyclo[9.4.2.1^{2,5}.1^{7,10}.0^{2,10}.0^{4,8}.0^{12,15}.0^{14,17}.0^{18,19}]nonadec-9-one (4c): from 0.55 g of **3c** (1.6 mmol) in 1.5 L of benzene, irradiation for 48 hrs: (> 90%). ^1H NMR (500 MHz, CDCl_3) $\delta = 7.40\text{--}7.35$ (m, 4H), overlaps 7.35-7.31 (m, 1H), 5.04 (dd, $J = 8.2, 4.1$ Hz, 1H), 4.80 (ddd, $J = 3.6, 1.8, 0.8$ Hz, 1H), 3.48 (dddd, $J = 5.5, 3.6, 1.8, 1.8$ Hz, 1H), 3.03 (t, $J = 6.7$ Hz, 1H), 2.89 (m, 2H), 2.74 (ddd, $J = 6.6, 1.8, 1.8$ Hz, 1H), overlaps 2.72 (m, 1H), 2.61-2.57 (m, 1H), overlaps 2.57-2.54 (ddd, $J = 8.2, 4.2, 1.9$ Hz, 1H), 2.10 (ddd, $J = 6.2, 6.2, 1.4$ Hz, 1H), 1.91 (dd, $J = 12.8, 1.8$ Hz, 1H), 1.87 (d, $J = 11.3$ Hz, 1H), 1.79 (ddd, $J = 12.9, 6.7, 1.9$ Hz, 1H), 1.65 (d, $J = 11.3$ Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) $\delta = 214.04, 136.85, 128.89, 128.67, 127.20, 101.02, 90.06, 86.83, 81.86, 56.46, 54.82, 54.68, 49.31, 47.00, 43.98, 42.34, 38.95, 37.22, 36.21, 35.68, 32.56$. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{21}\text{O}_3^+$ (MH^+) 345.1485, found 345.1472.

5. Preparation of the oxametathesis products (5-7):

(A) HCl-catalyzed formation of aldehydes 5: To a solution of oxetane **4** in DCM, a catalytic amount of HCl (4.0 *M* solution in dioxane) was added. The resulting mixture was stirred at room temperature for 24 h, washed twice with 5% solution of NaOH and water, concentrated, and purified on a silica gel column using hexane–ethyl acetate (or hexane–ethanol for the cyano-containing products). Usually this method produces an inseparable mixture of **5** and **6**.

(B1) BF₃ or (B2) HCl-catalyzed formation of aldehydes 6: BF₃·Et₂O (small molar excess per heteroatom in **4**) or >10-fold excess of HCl (4.0 *M* solution in dioxane) was added to a solution of oxetane **4** in DCM and stirred overnight at room temperature, washed twice with 5% solution of NaOH and water. The crude aldehyde **6** was purified on a silica gel column using hexane–ethyl acetate as an eluent. For cyano-containing aldehydes hexane–ethanol was used as the eluent.

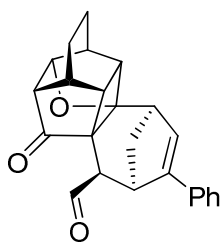
(C) Oxametathesis in alcohols yielding acetals 7: Oxetane **4** was dissolved in a 5% HCl solution in methanol, 4-bromobenzyl alcohol/DCM or ethylene glycol/THF and stirred for 24 h. The resulting mixture was evaporated, dissolved in DCM, washed twice with 5% solution of NaOH and water. The crude acetals **7** were purified on a silica gel column using hexane–ethyl acetate as an eluent. For cyano-containing acetals hexane–ethanol was used as the eluent. To avoid the hydrolysis of the cyano-containing acetals 2 mL of pyridine were passed through the column before purification.



1S(R), 8S(R), 9R(S), 12R(S), 13R(S)-**15-Cyano-14-oxo-11-phenyl-**

17-oxaheptacyclo[6.5.4.1^{9,12}.0^{1,8}.0^{2,7}.0^{3,15}.0^{6,16}]octadec-10-ene-13-carboxaldehyde (5a):

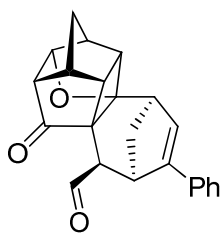
(method A) from 217 mg (0.56 mmol) of **4a** and 0.28 mL of HCl (4.0 M, 1.13 mmol) in DCM: forms a mixture of **5a** and **6a** (55.6% and 17.8% by NMR). ¹H NMR (500 MHz, CDCl₃) δ = 9.90 (s, 1H), 7.47 (d, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.30 (d, *J* = 3.4 Hz, 1H), 4.70 (d, *J* = 4.1 Hz, 1H), 3.82 (dd, *J* = 5.8, 4.7 Hz, 1H), 3.39 (d, *J* = 4.5 Hz, 1H), 2.86 (ddd, *J* = 8.5, 5.7, 1.5 Hz, 1H), 2.82 (dd, *J* = 4.8, 3.6 Hz, 1H), 2.64 (dd, *J* = 8.6, 4.8 Hz, 1H), 2.43-2.38 (m, 2H), 2.19 (m, 1H), 2.00-1.85 (m, 3H), 1.77 (d, *J* = 11.2 Hz, 1H), 1.57-1.50 (m, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 202.62, 200.08, 148.28, 134.45, 129.12, 128.98, 128.17, 126.63, 117.38, 87.81, 82.41, 56.60, 51.71, 46.95, 43.56, 40.48, 39.41, 37.51, 36.12, 35.03, 33.46, 16.01, 14.28. HRMS (ESI) calcd for C₂₅H₂₂NO₃⁺ (MH⁺) 384.1594, found 384.1590.



1S(R), 8S(R), 9R(S), 12R(S), 13R(S)-**14-Oxo-11-phenyl-17-**

oxaheptacyclo[6.5.4.1^{9,12}.0^{1,8}.0^{2,7}.0^{3,15}.0^{6,16}]octadec-10-ene-13-carboxaldehyde (5b):

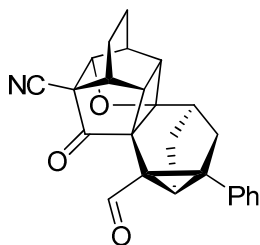
(method A) from 30 mg (0.08 mmol) of **4b** and 43 μL of HCl (4.0 M, 0.17 mmol) in DCM: forms a mixture of **5b**, **5b**^{*} (epimer) and **6b** (39.0%, 4.3% and 24.2% by NMR). Attempts to purify the mixture failed.



1S(R), 2R(S), 5R(S), 6R(S), 7S(R)-**16-Oxo-4-phenyl-13-**

oxaheptacyclo[5.5.4.1^{2,5}.0^{1,7}.0^{8,12}.0^{9,15}.0^{11,14}]heptadec-3-ene-6-carboxaldehyde (5c):

(method A) from 140 mg (0.41 mmol) of **4c** and 0.20 mL of HCl (4.0 M, 0.81 mmol) in DCM: forms a mixture of trace amount of **5c** and **6c**. Attempts to purify the mixture failed. ¹H NMR (500 MHz, CDCl₃) δ = 9.45 (d, *J* = 1.1 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.25 (m, 1H) overlaps with CDCl₃, 6.44 (d, *J* = 3.3 Hz, 1H), 4.96 (dd, *J* = 8.2, 4.1 Hz, 1H), 3.73 (dd, *J* = 5.7, 4.3 Hz, 1H), 3.20 (dd, *J* = 8.1, 5.9 Hz, 1H), 2.93 (dd, *J* = 5.0, 3.4 Hz, 1H), 2.85 (m, 1H), 2.81 (dd, *J* = 4.2, 1.0 Hz, 1H), 2.63-2.57 (m, 2H), 2.44 (ddd, *J* = 8.4, 5.3, 2.3 Hz, 1H), 2.38 (ddd, *J* = 11.0, 5.7, 5.0 Hz, 1H), 1.88 (d, *J* = 11.6 Hz, 1H), 1.85 (d, *J* = 11.4 Hz, 1H), 1.67 (d, *J* = 11.4 Hz, 1H).

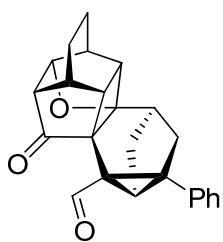


1S(R), 8S(R), 9R(S), 10S(R), 13R(S)-**16-Cyano-17-oxo-11-phenyl-**

14-oxaoctacyclo[6.5.4.1^{10,13}.0^{1,8}.0^{2,7}.0^{9,11}.0^{3,15}.0^{6,16}]octadec-9-carboxaldehyde (6a):

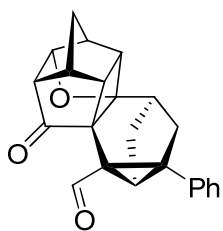
(method B1) from 390 mg (1.02 mmol) of **4a** and 2.00 mL of BF₃·Et₂O (48%, 15.86 mmol) in DCM (hexane/EtOH 10:1, then DCM/MeOH 2:1): 223 mg (57%). (method B2) from 200 mg (0.52 mmol) of **4a** and 2.61 mL of HCl (4.0 M, 10.43 mmol) in DCM (hexane/EtOH 10:1, then DCM/MeOH 2:1): 278 mg (71%). ¹H NMR (500 MHz, CDCl₃) δ = 8.41 (s, 1H), 7.38-7.30 (m, 5H), 4.74 (d, *J* = 4.1 Hz, 1H), 3.16 (ddd, *J* = 7.8, 5.9, 1.3

Hz, 1H), 2.89 (d, $J = 2.9$ Hz, 1H), 2.82 (m, 1H), 2.69 (dd, $J = 7.9, 5.0$ Hz, 1H), 2.52 (m, 1H), 2.27-2.18 (m, 5H), 2.11-2.04 (m, 1H), 2.02-1.96 (m, 2H), 1.72-1.65 (m, 1H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 200.43, 198.84, 137.60, 129.27, 128.99, 128.01, 117.41, 89.39, 82.69, 54.40, 52.37, 42.46, 40.09, 39.91, 37.74, 35.82, 35.73, 35.59, 34.57, 29.40, 28.18, 15.86, 14.31$. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{22}\text{NO}_3^+$ (MH^+) 384.1594, found 384.1592.



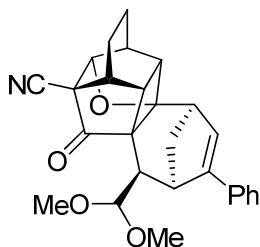
1S(R), 8S(R), 9R(S), 10S(R), 13R(S)-**17-Oxo-11-phenyl-14-oxaoctacyclo[6.5.4.1^{10,13}.0^{1,8}.0^{2,7}.0^{9,11}.0^{3,15}.0^{6,16}]octadec-9-carboxaldehyde (6b):**

(method B1) from 40 mg (0.11 mmol) of **4b** and 0.20 mL of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (48%, 1.59 mmol) in DCM (hexane/EtOH 10:1, then DCM/MeOH 2:1): 18 mg (45%). ^1H NMR (500 MHz, CDCl_3) $\delta = 8.39$ (s, 1H), 7.30 (m, 4H), 7.24 (m, 1H) overlaps with CDCl_3 , 4.56 (dd, $J = 8.1, 4.3$ Hz, 1H), 3.05 (ddd, $J = 7.8, 5.8, 1.3$ Hz, 1H), 2.81 (d, $J = 2.9$ Hz, 1H), 2.66 (ddd, $J = 8.2, 3.4, 2.2$ Hz, 1H), 2.56 (ddd, $J = 7.4, 4.9, 2.3$ Hz, 1H), 2.51 (d, $J = 12.3$ Hz, 1H), 2.43 (m, 1H), 2.19-2.13 (m, 4H), 2.06 (m, 1H), 1.94-1.87 (m, 1H), 1.84-1.72 (m, 2H), 1.57 (m, 1H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 199.53, 197.40, 138.40, 129.13, 129.11, 127.71, 88.52, 79.38, 55.16, 51.68, 42.39, 41.30, 40.08, 38.07, 36.00, 35.93, 35.91, 30.81, 29.71, 28.31, 17.78, 15.36$. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{O}_3^+$ (MH^+) 359.1642, found 359.1630.



1S(R), 2R(S), 3S(R), 6R(S), 7S(R)-**13-Oxo-4-phenyl-16-oxaoctacyclo[5.5.4.1^{3,6}.0^{1,7}.0^{2,4}.0^{8,12}.0^{9,15}.0^{11,14}]heptadec-2-carboxaldehyde (6c):**

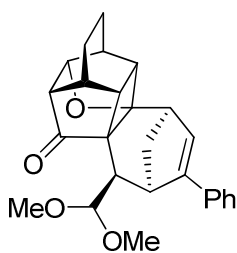
(method B1) and (method B2) failed. Under those conditions oxetane **4c** produced complicated mixture of inseparable compounds.



1S(R), 8S(R), 9R(S), 12R(S), 13R(S)-**15-Cyano-13-**

dimethoxymethyl-11-phenyl-17-oxaheptacyclo[6.5.4.1^{9,12}.0^{1,8}.0^{2,7}.0^{3,15}.0^{6,16}]octadec-10-ene-14-one (7a): (method C) from 320 mg (0.83 mmol) of **4a** and 3.13 mL of HCl (4.0 M, 12.52 mmol) in MeOH (hexane/EtOH 10:1, then DCM/MeOH 2:1): 258 mg (59%). ¹H NMR (500 MHz, CDCl₃) δ = 7.51 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.28 (d, *J* = 3.6 Hz, 1H), 4.67 (d, *J* = 4.1 Hz, 1H), 3.84 (d, *J* = 9.7 Hz, 1H), 3.29 (t, *J* = 5.3 Hz, 1H), 2.92 (dd, *J* = 9.7, 4.8 Hz, 1H), 2.87 (s, 3H) overlaps with 2.85 (ddd, *J* = 8.5, 5.8, 1.4 Hz, 1H), 2.79 (s, 3H), 2.72 (dd, *J* = 4.7, 3.8 Hz, 1H), 2.36 (dd, *J* = 8.5, 4.8 Hz, 1H), 2.30 (ddd, *J* = 11.1, 5.9, 5.1 Hz, 1H), 2.18 (m, 1H) overlaps with 2.15 (m, 1H), 1.96-1.87 (m, 3H), 1.67 (d, *J* = 11.2 Hz, 1H), 1.54-1.48 (m, 1H). ¹H NMR (500 MHz, C₆D₆) δ = 7.45 (d, *J* = 7.6 Hz, 2H), 7.17 (m, 2H) overlaps with C₆D₆, 7.08 (t, *J* = 7.4 Hz, 1H), 5.87 (d, *J* = 3.6 Hz, 1H), 4.35 (d, *J* = 4.1 Hz, 1H), 3.82 (d, *J* = 9.3 Hz, 1H), 3.18-3.13 (m, 2H), 2.70 (s, 3H), 2.66 (s, 3H), 2.55 (dd, *J* = 4.7, 3.8 Hz,

1H), 2.19 (ddd, $J = 8.5, 5.7, 1.4$ Hz, 1H), 2.05 (ddd, $J = 10.9, 5.4, 5.4$ Hz, 1H), 2.01 (m, 1H), 1.92 (dd, $J = 8.5, 4.8$ Hz, 1H), 1.73 (d, $J = 11.1$ Hz, 1H), 1.66-1.59 (m, 1H), 1.53 (m, 1H), 1.31-1.26 (m, 2H), 0.96-0.89 (m, 1H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 203.29, 149.49, 136.08, 128.61, 128.51, 128.20, 126.70, 117.79, 101.99, 88.02, 82.16, 57.93, 53.10, 52.16, 50.05, 43.55, 40.48, 39.31, 38.26, 35.94, 35.23, 34.76, 33.21, 16.14, 14.43$. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{27}\text{NNaO}_4^+$ (MNa^+) 452.1832, found 452.1810.

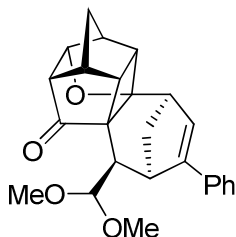


1S(R), 8S(R), 9R(S), 12R(S), 13R(S)-**13-Dimethoxymethyl-11-**

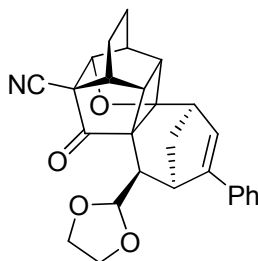
phenyl-17-oxaheptacyclo[6.5.4.1^{9,12}.0^{1,8}.0^{2,7}.0^{3,15}.0^{6,16}]octadec-10-ene-14-one (7b):

(method C) from 91 mg (0.25 mmol) of **4b** and 0.32 mL of HCl (4.0 M, 1.27 mmol) in MeOH (hexane/EtOH 20:1→10:1): 83 mg (81%). ^1H NMR (500 MHz, CDCl_3) $\delta = 7.53$ (d, $J = 7.4$ Hz, 2H), 7.32 (t, $J = 7.6$ Hz, 2H), 7.24 (t, $J = 7.4$ Hz, 1H) overlaps with CDCl_3 , 6.28 (d, $J = 3.5$ Hz, 1H), 4.53 (ddd, $J = 8.2, 4.3, 1.3$ Hz, 1H), 3.85 (d, $J = 9.8$ Hz, 1H), 3.27 (t, $J = 5.3$ Hz, 1H), 2.88 (dd, $J = 9.9, 4.8$ Hz, 1H) overlaps with 2.87 (s, 3H), 2.79 (ddd, $J = 8.5, 5.8, 1.5$ Hz, 1H), 2.76 (s, 3H), 2.70 (dd, $J = 4.8, 3.7$ Hz, 1H), 2.64 (ddd, $J = 8.3, 3.4, 2.2$ Hz, 1H), 2.28-2.23 (ddd, $J = 11.0, 5.3, 5.3$ Hz, 1H) overlaps with 2.28-2.23 (m, 1H), 2.04 (m, 1H), 1.89-1.74 (m, 3H), 1.71-1.65 (m, 1H) overlaps with 1.67 (d, $J = 10.9$ Hz, 1H), 1.48-1.41 (m, 1H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 213.35, 149.23, 136.60, 129.12, 128.47, 127.85, 126.74, 102.38, 87.06, 78.80, 58.51, 53.16,$

51.25, 49.75, 43.96, 41.66, 39.66, 38.39, 35.43, 34.38, 34.26, 30.55, 18.00, 15.46. HRMS (ESI) calcd for $C_{26}H_{28}NaO_4^+$ (MNa^+) 427.1880, found 427.1898.

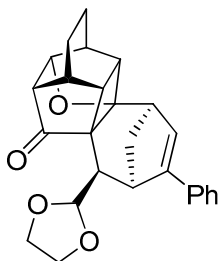


1S(R), 2R(S), 5R(S), 6R(S), 7S(R)-**6-Dimethoxymethyl-4-phenyl-13-oxaheptacyclo[5.5.4.1^{2,5}.0^{1,7}.0^{8,12}.0^{9,15}.0^{11,14}]heptadec-3-ene-16-one (7c)**: (method C) failed. Under those conditions oxetane **4c** produced complicated mixture.



1S(R), 8S(R), 9R(S), 12R(S), 13R(S)-**15-Cyano-13-(1,3-dioxolan-2-yl)-11-phenyl-17-oxaheptacyclo[6.5.4.1^{9,12}.0^{1,8}.0^{2,7}.0^{3,15}.0^{6,16}]octadec-10-ene-14-one (7a-1)**: (method C) from 190 mg (0.50 mmol) of **4a** and 1.24 mL of HCl (4.0 M, 4.95 mmol) in ethylene glycol/THF mixture (10/3) (hexane/EtOH 20:1→10:1): 148 mg (70%). 1H NMR (500 MHz, $CDCl_3$) δ = 7.63 (d, J = 7.3 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H) overlaps with $CDCl_3$, 6.44 (d, J = 3.6 Hz, 1H), 4.67 (d, J = 4.1 Hz, 1H), 4.46 (d, J = 9.1 Hz, 1H), 3.92-3.88 (m, 1H), 3.65 (m, 2H), 3.55-3.51 (m, 1H), 3.34 (dd, J = 5.7, 4.8 Hz, 1H), 2.82 (ddd, J = 8.4, 5.7, 1.4 Hz, 1H), 2.75 (dd, J = 4.7, 3.8 Hz, 1H), 2.70 (dd, J = 9.1, 4.6 Hz, 1H), 2.39 (dd, J = 8.4, 4.8 Hz, 1H), 2.27 (m, 2H), 2.17 (m, 1H), 1.97-1.86 (m, 3H), 1.65 (d, J = 11.1 Hz, 1H), 1.52-1.45 (m, 1H) overlaps with HOD. ^{13}C NMR (500 MHz, $CDCl_3$) δ = 203.09, 148.35, 135.36, 128.64,

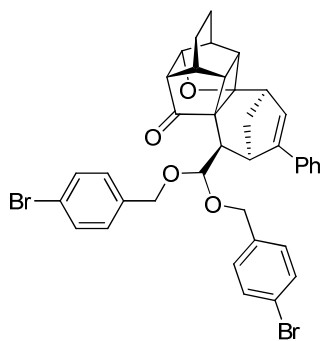
128.23, 127.98, 126.39, 117.91, 103.61, 87.58, 82.29, 65.02, 64.53, 57.15, 51.98, 43.43, 40.47, 38.66, 38.25, 38.20, 35.56, 35.19, 33.02, 16.09, 14.46. HRMS (ESI) calcd for $C_{27}H_{25}NNaO_4^+$ (MNa^+) 450.1676, found 450.1678.



1S(R), 8S(R), 9R(S), 12R(S), 13R(S)-**13-(1,3-Dioxalan-2-yl)-11-**

phenyl-17-oxaheptacyclo[6.5.4.1^{9,12}.0^{1,8}.0^{2,7}.0^{3,15}.0^{6,16}]octadec-10-ene-14-one (7b-1):

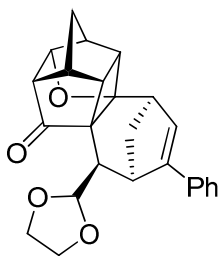
(method C) from 180 mg (0.50 mmol) of **4b** and 0.32 mL of HCl (4.0 M, 1.26 mmol) in ethylene glycol/THF mixture (10/3) (hexane/EtOAc 25:1): 158 mg (78%). 1H NMR (500 MHz, $CDCl_3$) δ = 7.64 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H) overlaps with $CDCl_3$, 6.46 (d, J = 3.6 Hz, 1H), 4.53 (ddd, J = 8.1, 4.2, 1.4 Hz, 1H), 4.47 (d, J = 9.1 Hz, 1H), 3.92-3.87 (m, 1H), 3.66-3.59 (m, 2H), 3.53-3.49 (m, 1H), 3.32 (dd, J = 5.7, 4.7 Hz, 1H), 2.76 (ddd, J = 8.2, 5.6, 1.5 Hz, 1H), 2.72 (dd, J = 4.6, 3.9 Hz, 1H), 2.68 (dd, J = 9.1, 4.6 Hz, 1H), 2.63 (ddd, J = 8.2, 3.3, 2.1 Hz, 1H), 2.28 (ddd, J = 8.3, 4.7, 2.1 Hz, 1H), 2.24 (ddd, J = 11.0, 5.5, 5.5 Hz, 1H), 2.04 (m, 1H), 1.91 (m, 1H), 1.88-1.81 (m, 1H), 1.79-1.72 (m, 1H), 1.70-1.63 (m, 1H) overlaps with 1.66 (d, J = 10.8 Hz, 1H), 1.45-1.38 (dddd, J = 13.8, 11.8, 5.9, 2.5 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ = 213.24, 148.08, 135.89, 128.63, 128.51, 127.88, 126.41, 104.01, 86.60, 78.97, 64.75, 64.33, 57.68, 51.08, 43.85, 41.66, 38.98, 38.47, 37.61, 35.37, 33.99, 30.18, 17.98, 15.49. HRMS (ESI) calcd for $C_{26}H_{27}O_4^+$ (MH^+) 403.1904, found 403.1903.



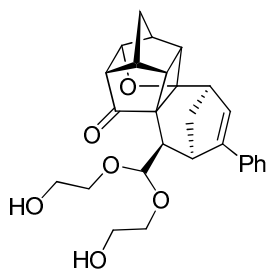
1S(R), 8S(R), 9R(S), 12R(S), 13R(S)-15-Cyano-13-bis-(4-bromobenzyloxymethyl)-11-phenyl-17-

oxaheptacyclo[6.5.4.1^{9,12}.0^{1,8}.0^{2,7}.0^{3,15}.0^{6,16}]octadec-10-ene-14-one (**7b-2**): (method C)

from 200 mg (0.56 mmol) of **4b**, 0.37 g (1.95 mmol) of 4-bromobenzyl alcohol and 0.35 mL of HCl (4.0 M, 1.39 mmol) in DCM (hexane/EtOAc 20:1→10:1): 215 mg (54%). ¹H NMR (500 MHz, CDCl₃) δ = 7.46-7.43 (m, 4H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.22-7.17 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.27 (d, *J* = 3.5 Hz, 1H), 4.52 (ddd, *J* = 8.2, 4.3, 1.3 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 1H) overlaps with 4.27 (d, *J* = 9.9 Hz, 1H), 4.10 (m, 2H), 3.51 (d, *J* = 12.1 Hz, 1H), 3.34 (dd, *J* = 5.7, 4.8 Hz, 1H), 3.12 (dd, *J* = 9.9, 4.7 Hz, 1H), 2.79 (ddd, *J* = 8.3, 5.7, 1.4 Hz, 1H), 2.72 (dd, *J* = 4.6, 3.7 Hz, 1H), 2.59 (ddd, *J* = 8.1, 2.5, 2.5 Hz, 1H), 2.29 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1H), 2.18 (ddd, *J* = 8.4, 4.3, 2.0 Hz, 1H), 2.04 (m, 1H), 1.88-1.80 (m, 1H), 1.76-1.69 (m, 1H) overlaps with 1.71 (d, *J* = 11.0 Hz, 1H), 1.58-1.55 (m, 2H), 1.35-1.28 (m, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 213.53, 148.98, 137.51, 136.95, 136.70, 131.49, 131.46, 129.70, 129.59, 128.48, 128.43, 127.85, 126.73, 121.43, 121.09, 100.47, 86.96, 78.78, 65.40, 63.48, 58.39, 51.08, 43.94, 41.63, 39.96, 38.30, 35.33, 34.82, 34.09, 30.34, 17.81, 15.31. HRMS (ESI) calcd for C₃₈H₃₈Br₂NO₄⁺ (MNH₄⁺) 732.1147, found 732.1149.



1S(R), 2R(S), 5R(S), 6R(S), 7S(R)-6-(1,3-Dioxolan-2-yl)-4-phenyl-13-oxaheptacyclo[5.5.4.1^{2,5}.0^{1,7}.0^{8,12}.0^{9,15}.0^{11,14}]heptadec-3-ene-16-one (**7c-1**): (method C produced a mixture of **7c-1** and **7c-2** 3:1) from 210 mg (0.61 mmol) of **4c** and 0.30 mL of HCl (4.0 M, 1.22 mmol) in ethylene glycol/THF mixture (10/3) (hexane/EtOAc 20:1→10:1, then hexane/EtOH 10:1 to get **7c-2**): 71 mg (< 30%, major loss is on the column). ¹H NMR (500 MHz, CDCl₃) δ = 7.63 (d, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H) overlaps with CDCl₃, 6.47 (d, *J* = 3.6 Hz, 1H), 4.99 (dd, *J* = 8.2, 4.0 Hz, 1H), 4.49 (d, *J* = 9.1 Hz, 1H), 3.91-3.88 (m, 1H), 3.68-3.61 (m, 2H), 3.55-3.51 (m, 1H), 3.33 (dd, *J* = 5.6, 4.8 Hz, 1H), 2.90 (ddd, *J* = 7.9, 6.2, 1.4 Hz, 1H), 2.75 (m, 2H), 2.67 (dd, *J* = 9.1, 4.6 Hz, 1H), 2.62-2.58 (ddd, *J* = 8.2, 4.3, 1.8 Hz, 1H) overlaps with 2.57 (m, 1H), 2.51 (ddd, *J* = 8.4, 5.2, 1.7 Hz, 1H), 2.25 (ddd, *J* = 10.9, 5.5, 5.5 Hz, 1H), 1.84 (d, *J* = 11.3 Hz, 1H), 1.65 (d, *J* = 10.8 Hz, 1H) overlaps with 1.62 (d, *J* = 11.3 Hz, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 214.75, 148.08, 135.85, 128.78, 128.51, 127.90, 126.43, 103.85, 87.18, 86.44, 64.85, 64.34, 56.77, 54.25, 48.16, 47.36, 43.92, 42.08, 38.96, 38.79, 38.29, 37.67, 36.32. HRMS (ESI) calcd for C₂₅H₂₅O₄⁺ (MH⁺) 389.1747, found 389.1761.



1S(R), 2R(S), 5R(S), 6R(S), 7S(R)-**6-(bis-(2-**

hydroxyethoxy)methyl)-4-phenyl-13-

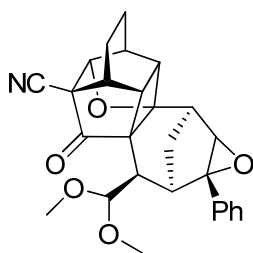
oxaheptacyclo[5.5.4.1^{2,5}.0^{1,7}.0^{8,12}.0^{9,15}.0^{11,14}]heptadec-3-ene-16-one (**7c-2**):

(hexane/EtOH 10:1): 23 mg (< 10%). ¹H NMR (500 MHz, CDCl₃) δ = 7.48 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H) overlaps with CDCl₃, 6.28 (d, *J* = 3.5 Hz, 1H), 5.00 (dd, *J* = 8.3, 4.0 Hz, 1H), 4.15 (d, *J* = 9.6 Hz, 1H), 3.65 (ddd, *J* = 11.9, 7.6, 2.8 Hz, 1H), 3.56 (ddd, *J* = 11.9, 4.8, 2.9 Hz, 1H), 3.51-3.43 (m, 2H), 3.40 (ddd, *J* = 10.2, 7.7, 2.9 Hz, 1H), 3.28 (dd, *J* = 5.8, 4.9 Hz, 1H) overlaps with 3.26 (m, 2H), 2.96 (ddd, *J* = 7.8, 6.3, 1.2 Hz, 1H) overlaps with 2.94 (dd, *J* = 9.7, 4.6 Hz, 1H), 2.78 (m, 1H), 2.74 (dd, *J* = 4.7, 3.7 Hz, 1H), 2.68 (ddd, *J* = 10.0, 4.8, 2.8 Hz, 1H), 2.62 (ddd, *J* = 8.4, 4.3, 1.8 Hz, 1H), 2.58 (m, 1H), 2.55 (ddd, *J* = 8.2, 5.4, 1.7 Hz, 1H), 2.30 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1H), 1.86 (d, *J* = 11.3 Hz, 1H), 1.67 (d, *J* = 11.2 Hz, 1H) overlaps with 1.66 (d, *J* = 11.0 Hz, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 215.41, 149.21, 136.88, 129.72, 128.57, 128.03, 126.72, 101.02, 87.20, 86.96, 66.09, 64.35, 62.21, 62.18, 57.66, 54.44, 48.18, 47.43, 44.07, 42.29, 39.95, 38.82, 37.82, 36.42, 35.80. HRMS (ESI) calcd for C₂₇H₃₀NaO₆⁺ (MNa⁺) 473.1935, found 473.1938.

6. Preparation of the oxiranes (8):

Approximately 2.0-50 mM solution of a precursor **7** in benzene or DCM was irradiated in Pyrex or glass reaction vessels in a Rayonet reactor equipped with RPR-

3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) for 3-24 hours. Irradiation resulted in a quantitative conversion to **8**. The resulting crude product was purified on a silica gel column using a mixture of hexane and EtOH as an eluent.



1S(R), 2R(S), 11S(R), 12R(S), 13S(R), 14S(R), 16S(R)-**9-Cyano-12-**

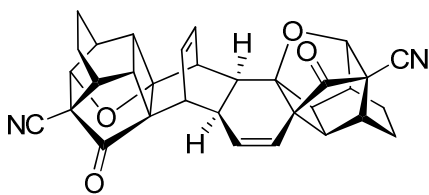
dimethoxymethyl-14-phenyl-3,15-

dioxaoctacyclo[11.3.1.1^{2,5}.1^{8,11}.0^{2,11}.0^{4,9}.0^{14,16}.0^{18,19}]nonadec-10-one (8a): from 46 mg of **7a** (0.11 mmol) in 0.6-2.0 mL of benzene or DCM (C₆D₆ or CDCl₃ for an NMR experiment), irradiation for 5-24 hrs. ¹H NMR (500 MHz, CDCl₃) δ = 7.51 (m, 2H), 7.45-7.38 (m, 3H), 4.70 (d, *J* = 4.2 Hz, 1H), 3.94 (s, 1H), 3.57 (d, *J* = 10.0 Hz, 1H), 3.42 (ddd, *J* = 8.6, 5.9, 1.2 Hz, 1H), 3.01 (t, *J* = 5.5 Hz, 1H), 2.88 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.81 (s, 3H), 2.69 (s, 3H), 2.51 (dd, *J* = 4.7, 1.5 Hz, 1H), 2.45 (dd, *J* = 8.6, 4.8 Hz, 1H), 2.30 (m, 1H), 2.18 (m, 1H), 2.06-1.96 (m, 3H), 1.91 (ddd, *J* = 11.9, 5.9, 5.0 Hz, 1H), 1.65-1.59 (m, 1H) overlaps with HOD, 1.08 (d, *J* = 12.0 Hz, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 201.76, 135.56, 129.11, 128.83, 117.23, 100.21, 90.95, 80.88, 65.88, 58.22, 57.22, 53.32, 51.53 (m), 49.45, 48.26 (m), 38.61, 38.51, 36.67, 36.18, 35.33, 35.21, 32.67, 27.67, 15.68, 14.04. ¹H NMR (500 MHz, C₆D₆) δ = 7.30 (m, 2H), 7.09-7.03 (m, 3H), 4.26 (d, *J* = 4.2 Hz, 1H), 3.58 (d, *J* = 10.0 Hz, 1H), 3.47 (s, 1H), 3.05 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.94 (dd, *J* = 6.0, 5.0 Hz, 1H), 2.64 (s, 3H), 2.58 (ddd, *J* = 8.5, 5.7, 1.2 Hz,

1H), 2.48 (s, 3H), 2.32 (dd, $J = 4.6, 1.3$ Hz, 1H), 2.12 (dd, $J = 8.6, 4.8$ Hz, 1H), 2.02 (m, 1H), 1.90 (ddd, $J = 11.5, 6.0, 5.0$ Hz, 1H), 1.64-1.57 (m, 1H), 1.44 (m, 1H), 1.30-1.26 (m, 2H), 1.10 (d, $J = 11.8$ Hz, 1H), 0.91-0.83 (m, 1H). ^{13}C NMR (500 MHz, C_6D_6) $\delta = 202.15, 137.13, 129.09, 129.05, 127.86, 117.82, 100.61, 91.28, 81.28, 66.05, 58.29, 57.78, 53.17, 52.48, 49.14, 39.43, 38.63, 37.37, 36.64, 35.87, 35.51, 33.07, 28.35, 16.07, 14.28$. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{27}\text{KNO}_5^+$ (MK^+) 484.1521, found 484.1530.

7. Preparation of the dimers (9):

A solution of **2** in 5-10 mL of 1,2-dichlorobenzene was heated in a bomb at 200-210°C for 24-72 hours. After the reaction was cooled to room temperature, the solvent was removed on a high vacuum pump. The crude reaction mixture was purified on a silica gel column using a mixture of hexane and EtOAc (hexane/EtOH and DCM/MeOH in case of **2a**) as an eluent.



1S(R), 2R(S), 5R(S), 14R(S), 15S(R), 16S(R), 17R(S),

26R(S)-7,24-Dicyano-13,18-

dioxatridecacyclo[14.10.2.1^{5,8}.1^{11,14}.1^{17,20}.1^{23,26}.0^{2,15}.0^{5,14}.0^{7,12}.0^{17,26}.0^{19,24}.0^{29,30}.0^{31,32}]dot

riaconta-3,27-diene-6,25-dione (9a): from 0.46 g of **2a** (1.8 mmol) in 10 mL of 1,2-

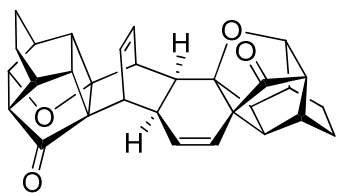
dichlorobenzene at 210°C for 72 hrs (hexane/EtOH gradient 10:1→1:1 and DCM/MeOH

5:1): 0.15 g (33%). ^1H NMR (500 MHz, CDCl_3) $\delta = 6.19$ (ddd, $J = 8.0, 6.4, 1.1$ Hz, 1H),

6.13 (ddd, $J = 8.1, 6.9, 1.4$ Hz, 1H), 5.75 (dd, $J = 10.4, 2.8$ Hz, 1H), 5.55 (dd, $J = 10.4,$

2.3 Hz, 1H), 4.71 (d, $J = 4.1$ Hz, 1H), 4.64 (d, $J = 4.1$ Hz, 1H), 3.38 (dddd, $J = 9.1, 2.7,$

2.7, 2.7 Hz, 1H), 3.15 (d, $J = 6.8$ Hz, 1H), 2.81 (ddd, $J = 6.3, 2.7, 1.5$ Hz, 1H), 2.74 (ddd, $J = 8.3, 5.5, 1.2$ Hz, 1H), 2.64 (ddd, $J = 7.4, 5.8, 1.4$ Hz, 1H), 2.50 (dd, $J = 9.1, 1.5$ Hz, 1H), 2.25 (m, 3H), 2.15 (dd, $J = 8.4, 5.2$ Hz, 1H), 2.11 (m, 1H) overlaps with 2.08 (dd, $J = 7.7, 5.0$ Hz, 1H), 1.94-1.82 (m, 6H), 1.57-1.45 (m, 2H). ^{13}C NMR (400 MHz, CDCl_3) $\delta = 202.75, 201.31, 133.35, 133.33, 131.83, 120.07, 117.40, 117.38, 91.20, 85.42, 83.12, 80.50, 56.91, 55.50, 53.30, 52.59, 43.30, 39.67, 37.13, 37.00, 36.41, 35.86, 35.80, 35.74, 35.16, 35.10, 34.00, 33.79, 16.05, 15.93, 14.23, 14.06$. HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{30}\text{N}_3\text{O}_4^+$ (MNH_4^+) 520.2231, found 520.2232.



1S(R), 2R(S), 5R(S), 14R(S), 15S(R), 16S(R), 17R(S), 26R(S)-

13,18-

Dioxatridecacyclo[14.10.2.1^{5,8}.1^{11,14}.1^{17,20}.1^{23,26}.0^{2,15}.0^{5,14}.0^{7,12}.0^{17,26}.0^{19,24}.0^{29,30}.0^{31,32}]dot

riaconta-3,27-diene-6,25-dione (9b): from 170 mg of **2b** (0.75 mmol) in 5 mL of 1,2-

dichlorobenzene at 200 °C for 24 hrs (hexane/EtOAc gradient 20:1→4:1): 41 mg (24%).

^1H NMR (500 MHz, CDCl_3) $\delta = 6.20$ (m, $J = 7.3$ Hz, 1H), 6.12 (m, $J = 7.5$ Hz, 1H), 5.71

(dd, $J = 10.5, 2.8$ Hz, 1H), 5.54 (dd, $J = 10.3, 2.2$ Hz, 1H), 4.56 (dd, $J = 7.6, 4.1$ Hz,

1H), 4.47 (dd, $J = 8.0, 4.0$ Hz, 1H), 3.39 (dddd, $J = 8.6, 2.7, 2.7, 2.7$ Hz, 1H), 3.15 (d, J

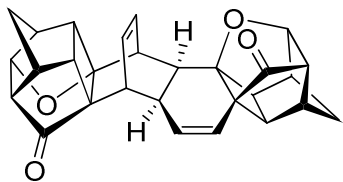
$= 6.7$ Hz, 1H), 2.73 (d, $J = 6.3$ Hz, 1H), 2.66 (dd, $J = 8.3, 5.6$ Hz, 1H), 2.57-2.49 (m,

4H), 2.10 (m, 1H), 2.02 (ddd, $J = 7.8, 5.1, 2.4$ Hz, 1H), 1.98 (m, 1H), 1.94 (m, 1H), 1.90

(m, 2H), 1.85-1.69 (m, 4H), 1.67-1.59 (m, 2H), 1.47-1.36 (m, 2H). ^{13}C NMR (500 MHz,

CDCl_3) $\delta = 213.87, 212.78, 133.40, 132.98, 131.77, 121.21, 90.38, 84.79, 79.65, 77.02,$

57.53, 56.47, 52.91, 52.18, 44.71, 40.80, 37.74, 37.40, 37.37, 36.54, 35.90, 35.36, 35.11, 34.25, 31.20, 30.09, 18.08, 17.90, 15.37, 15.18. HRMS (ESI) calcd for $C_{30}H_{29}O_4^+$ (MH^+) 453.2060, found 453.2077.



1S(R), 2R(S), 5R(S), 14R(S), 15S(R), 16S(R), 17R(S), 26R(S)-

13,18-

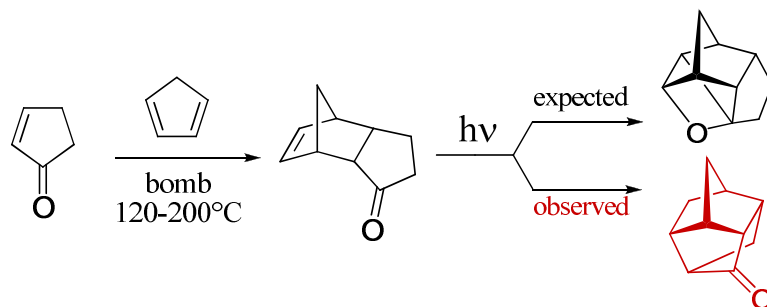
Dioxatridecacyclo[14.10.2.1^{8,11}.1^{20,23}.0^{2,15}.0^{5,9}.0^{5,14}.0^{7,12}.0^{10,14}.0^{17,21}.0^{17,26}.0^{19,24}.0^{22,26}]trien-3,27-diene-6,25-dione (9c): from 0.56 g of **2c** (2.6 mmol) in 10 mL of 1,2-dichlorobenzene at 210 °C for 48 hrs (hexane/EtOAc gradient 20:1→10:1): 0.45 g (80%). ¹H NMR (500 MHz, CDCl₃) δ = 6.20 (ddd, *J* = 7.9, 6.5, 1.1 Hz, 1H), 6.11 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 5.71 (dd, *J* = 10.4, 2.8 Hz, 1H), 5.54 (dd, *J* = 10.4, 2.3 Hz, 1H), 5.02 (ddd, *J* = 8.0, 3.1, 2.2 Hz, 1H), 4.94 (dd, *J* = 8.4, 3.8 Hz, 1H), 3.35 (dddd, *J* = 9.1, 2.7, 2.7, 2.7 Hz, 1H), 3.18 (d, *J* = 6.9 Hz, 1H), 2.85-2.79 (m, 2H), 2.76 (ddd, *J* = 6.4, 2.7, 1.4 Hz, 1H), 2.73-2.69 (m, 2H), 2.59 (m, 2H), 2.51 (dd, *J* = 9.3, 1.5 Hz, 1H), 2.47 (ddd, *J* = 8.4, 4.2, 2.0 Hz, 1H), 2.42 (ddd, *J* = 8.0, 4.2, 1.9 Hz, 1H), 2.20 (ddd, *J* = 7.8, 5.6, 2.0 Hz, 1H), 2.09 (m, 1H), 1.81 (d, *J* = 11.3 Hz, 1H), 1.75 (d, *J* = 11.3 Hz, 1H), 1.61 (d, *J* = 11.3 Hz, 1H), 1.52 (d, *J* = 11.3 Hz, 1H). ¹H NMR (500 MHz, C₆D₆) δ = 6.21 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 6.04 (ddd, *J* = 7.8, 6.5, 1.2 Hz, 1H), 5.75-5.68 (m, 2H), 4.59 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.53 (ddd, *J* = 8.5, 2.6, 2.6 Hz, 1H), 3.80 (dddd, *J* = 9.3, 2.5, 2.5, 2.5 Hz, 1H), 3.50 (d, *J* = 7.0 Hz, 1H), 2.84 (dd, *J* = 9.3, 1.6 Hz, 1H), 2.64 (ddd, *J* = 6.3, 2.8, 1.4 Hz, 1H), 2.27 (ddd, *J* = 7.4, 6.2, 1.2 Hz, 1H), 2.23-2.18 (m, 3H), 2.17-2.13 (m, 2H),

2.05 (m, 1H), 1.99 (m, 1H), 1.78 (m, $J = 5.5, 2.5$ Hz, 1H), 1.62 (ddd, $J = 7.4, 5.5, 1.9$ Hz, 1H), 1.14-1.10 (m, 2H), 0.97 (m, 2H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 214.68, 214.07, 133.72, 132.94, 131.74, 121.28, 90.69, 87.79, 85.40, 84.86, 56.42, 55.27, 54.96, 54.31, 51.27, 48.22, 47.29, 47.22, 41.99, 41.24, 40.80, 38.34, 37.88, 37.33, 37.15, 36.62, 36.21, 34.03$. HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{25}\text{O}_4^+$ (MH^+) 425.1747, found 425.1748.

Chapter Four: Photoprotolytic transformations in the aliphatic series

A. Introduction.

Polycyclic enones resulting from the *Diels-Alder* adducts of aliphatic unsaturated ketones undergo photocyclizations to furnish remarkably strained oxetane systems. These systems were extensively studied by Sauers and co-workers in 1972 - 1974 [36], who discovered the multitude of synthetic applications that they could offer. This research, however, came to a dead end when they introduced cyclic ketones to the system, giving a fused norbornene derivative containing a tricyclo[5.2.1.0^{2,6}] core.

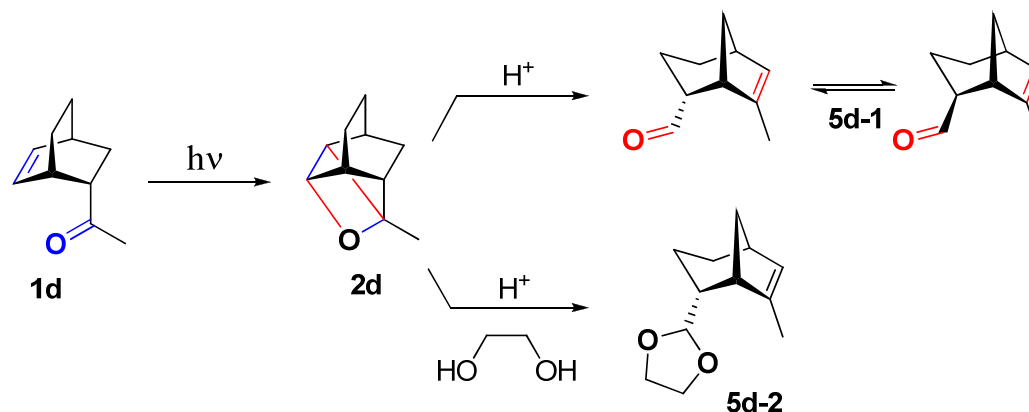


They found that these systems were unable to undergo the *Paternò-Büchi* cycloaddition that had been observed in so many other analogs. It was discovered that upon irradiation tricyclo[5.2.1.0^{4,9}]undecan-5-one was produced instead of the expected oxetane [36b]. This finding could be explained based on the fact that n-orbital of the carbonyl group in such a highly strained and rigid tricycle simply cannot reach the double bond. Instead,

energy transfer from the excited carbonyl to the double bond occurs first, which causes further α -H abstraction by the double bond and subsequent collapse of a newly formed 1,5-diradical. Upon further investigation, we were able to find that when the system was provided with a bit more conformational flexibility, a profound range of possibilities opened up.

B. Results and discussion.

First, we decided to prepare model aliphatic oxetanes with a “flexible” or “free” methyl group based on the *D.-A.* adducts of cyclohexadiene or cyclopentadiene with methyl vinyl ketone. Upon addition of HCl the expected oxametathesis occurred (Scheme 30), similar to the results observed in aromatic series [30] and chromone-based series [34].

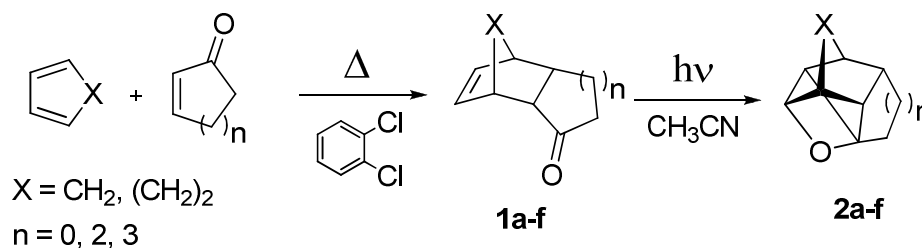


Scheme 30. An alkene-carbonyl oxametathesis in “flexible” aliphatic series.

These results might not have a very significant synthetic application, yet they confirm the generality of the methodology we have developed in the past two years.

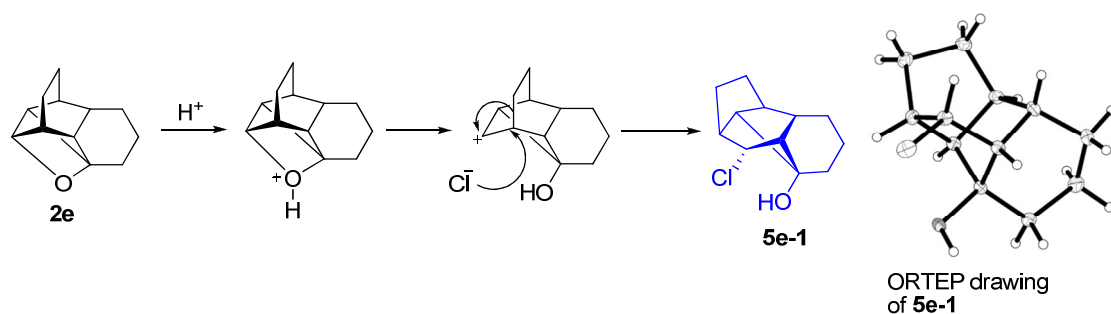
We further proposed, that polycyclic scaffolds resulting from the *D.-A.* adducts of cyclic ketones may have the capability of undergoing photocyclization to furnish

remarkably strained oxetane systems. Although Sauer's observation was discouraging, upon additional investigation we were able to find that systems with more conformational freedom were highly reactive. Probing new combinations of adducts not only gave us the opportunity to make highly strained oxetane systems, but also elucidation of the mechanism of their protolytic ring opening provided a great deal of insight into how the strain affects the system. We aimed to harness this installed strain as a means for synthesizing unique aliphatic polycycles (Scheme 31):



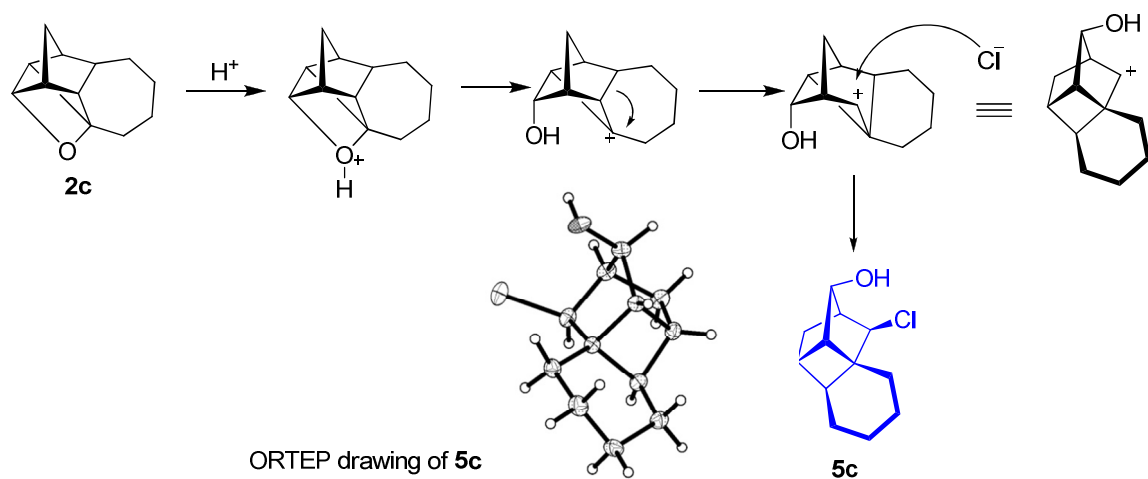
Scheme 31. Polycyclic scaffolds resulting from the *D.-A.* adducts of aliphatic ketones (**1**) and the *P.-B.* photocyclization (**2**).

After synthesizing “6-6 adduct” **1e** (Experimental Section, page 103) based on cyclohexadiene and 2-cyclohexen-1-one, it was converted into oxetane **2e** upon irradiation. We found that, upon the addition of HCl, oxetane **2e** opened to give the secondary carbocation rather than tertiary. We suppose this is due to the inability of the structure to accommodate a planar conformation at the tertiary center. Upon nucleophilic attack, 1,2-alkyl shift occurred to give the final product **5e-1**, which we were able to confirm by X-ray diffraction (Scheme 32):



Scheme 32. A plausible mechanism of the formation of **5e-1**.

However, the situation changed dramatically when another “5-7 adduct” **1c** (Experimental Section, page 102) was synthesized. Its oxetane, **2c**, opened in an orthogonal way. The formation of a tertiary carbocation was preferred likely because of the extra flexibility offered by the installed seven-membered ring (Scheme 33):



Scheme 33. A plausible mechanism of the formation of **5c**.

Such a tertiary carbocation resembles the tricyclooctane core (Figure 13). These tricyclo[3.3.0.0^{3,7}]octanes are known to have very high ring strain energies [37].

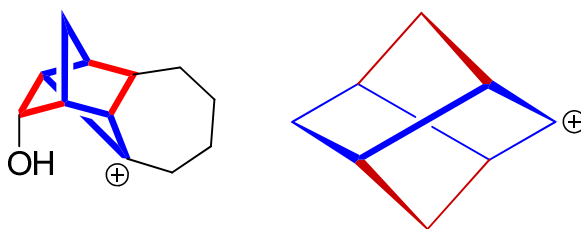


Figure 13. Tertiary tricyclo[3.3.0.0^{3,7}]octanyl cation formed during the formation of rearranged product **5c**.

The carbocation (Figure 13), which most likely was produced during the formation of **5c**, as a result of high ring strain, rearranged notably producing a new cyclobutane. The X-ray structure of **5c** and the mechanism of the rearrangement are shown in Scheme 33.

With this in mind, we have synthesized a variety of adducts from very simple starting dienes and dienophiles using the same basic procedure throughout (Figure 14-1). The starting materials were combined in a bomb with a minimal amount of dichlorobenzene as the solvent. They were then heated to roughly 200°C overnight. After purification by column chromatography, the pure product was irradiated in an RPR-3000 broadband (250 - 300 nm) Rayonet photoreactor. The oxetanes were then treated with a variety of acidic conditions (Lewis acids, formic acid, HCl, etc.) and the ring opening products were isolated via column chromatography (for more details please see Experimental Section, page 100-115).

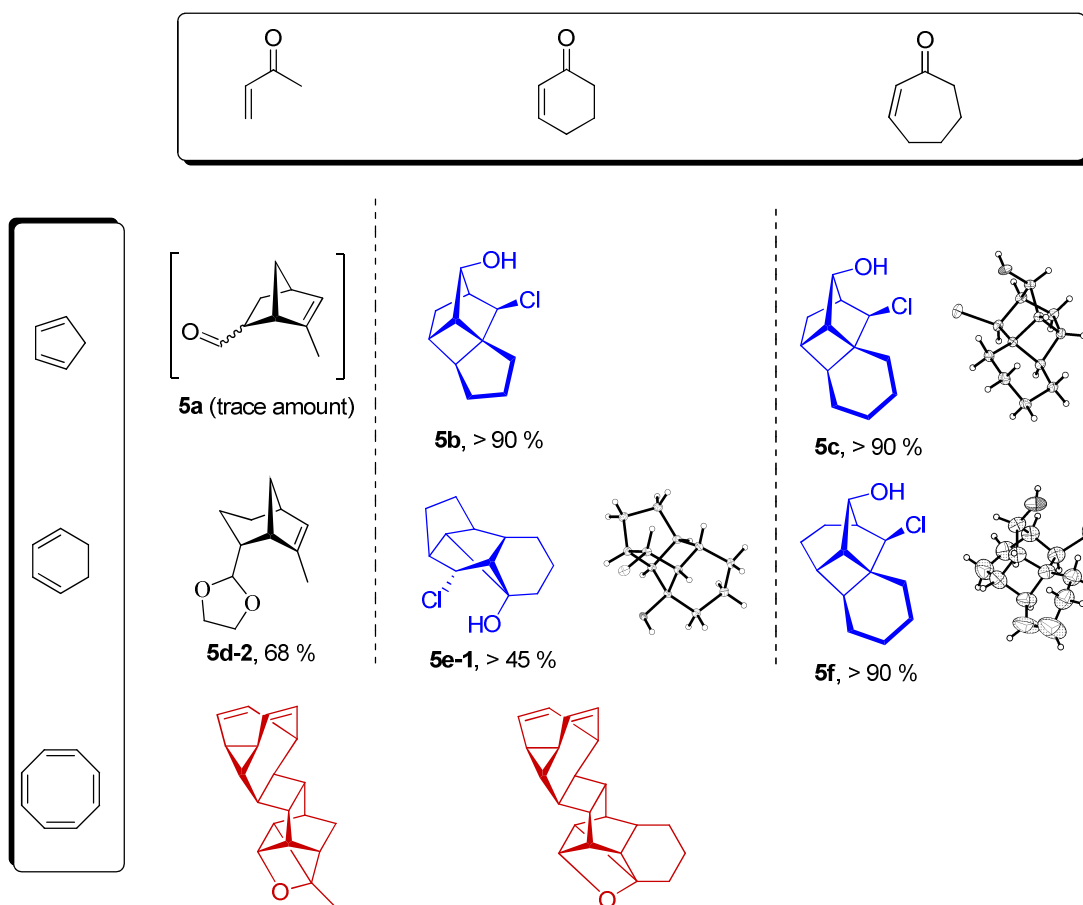


Figure 14-1. Various rearranged products obtained from polycyclic oxetanes **2**.

We also discovered that, in reactions with weak dienophiles, cyclooctatetraene (COT) often yielded 2:1 adducts possessing the fluxional bicyclo[5.1.0]octadiene moiety. They undergo a fast, nearly degenerate Cope rearrangement with an activation barrier similar to that of the parent dihydrobullvalene. Irradiation, conditioned to excite the carbonyl moiety, induces the intramolecular *P.-B.* cyclization yielding *endo*-oxetanes and significantly changing the *Cope*-averaged NMR spectra (Figure 14-1 and 14-2). Hypothetically, due to the reversible nature of the oxetane formation, this system may offer a way of controlling molecular properties with a photoinduced switch [38].

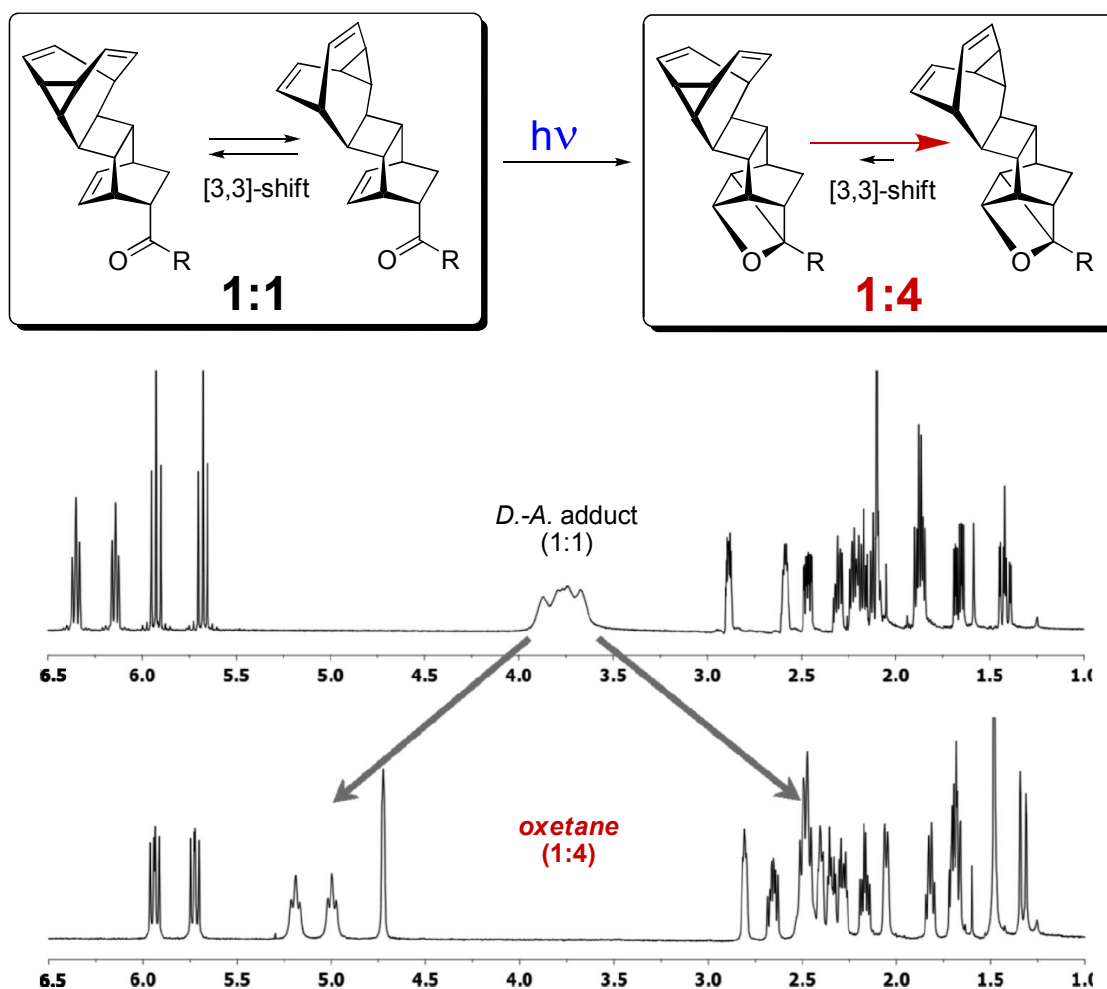
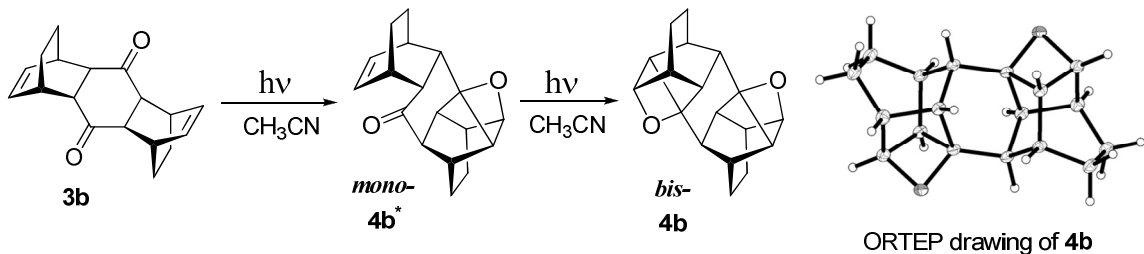


Figure 14-2. NMR changes upon photoconversion of the *D.-A.* adduct (1:1) to the *P.-B.* adduct (1:4) [38].

The next logical step was to study strained oxetanes containing more than one oxetane unit. Benzoquinone's *bis-D.-A.* adducts with cyclopentadiene and cyclohexadiene were known before [39]. However, the photochemistry of these promising compounds had not been studied and it was not known whether they form oxetanes upon irradiation. We were able to synthesize several bis-adducts using cyclopentadiene, cyclohexadiene, and cyclooctatetraene as the dienes. Successful

irradiation results were found in the case of adducts of benzoquinone with cyclohexadiene **3b** (Scheme 34):



Scheme 34. Preparation of *bis*-oxetane **4b** and its ORTEP drawing.

Surprisingly dioxetane molecules **4b** pack in a crystal lattice in such a way that they form six-pointed geometric figure, also known as a hexagram. Such unusual packing leads to channel formation (a diameter of 0.7 – 0.9 nm; see Figure 15) throughout the crystal lattice where a solvent molecule (here, CH₃CN) can be trapped.

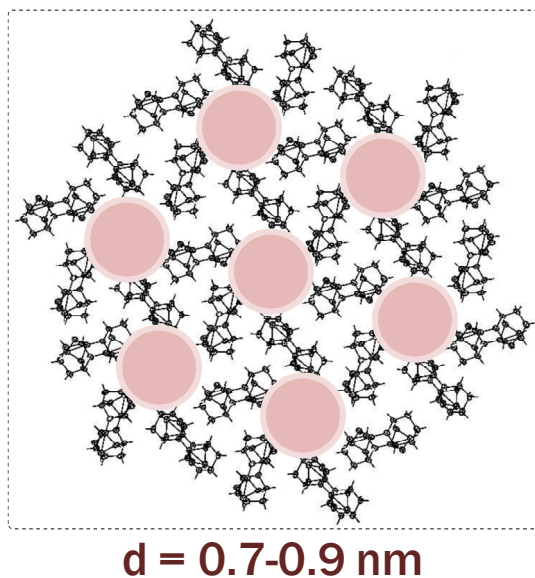


Figure 15. Packing of *bis*-oxetane **4b** in a crystal lattice.

It should be noted that in our work we also used computational prediction for ¹H and ¹³C NMR's of unknown compounds. It was especially important for cases when X-

ray data were not available. The geometry was optimized at the B3LYP/6-311+G(d,p) level and then a single point calculation at the mPW1PW91/6-311+G(d,p) level was performed. To illustrate the accuracy of this approach (especially for rigid molecules with restricted conformational freedom) two NMR spectra of *bis*-oxetane **4b** are shown below (Figure 16). The upper spectrum is the experimental ^1H NMR. The lower NMR spectrum predicted at the mPW1PW91/6-311+G(d,p)//B3LYP/6-311+G(d,p) level of theory matches the experimental data almost perfectly.

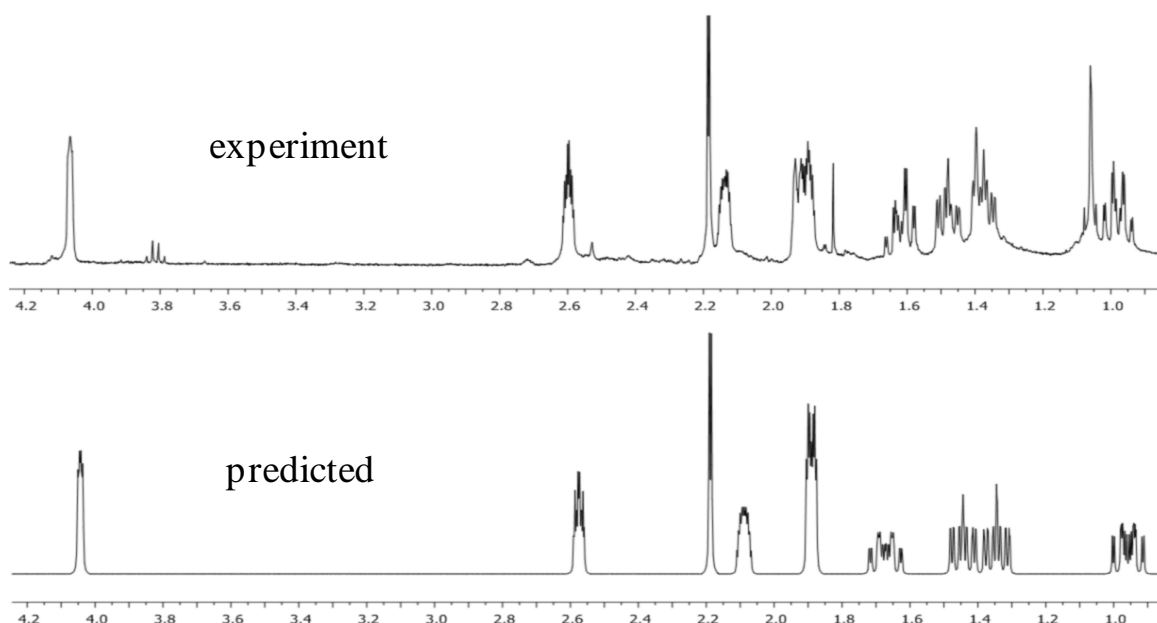
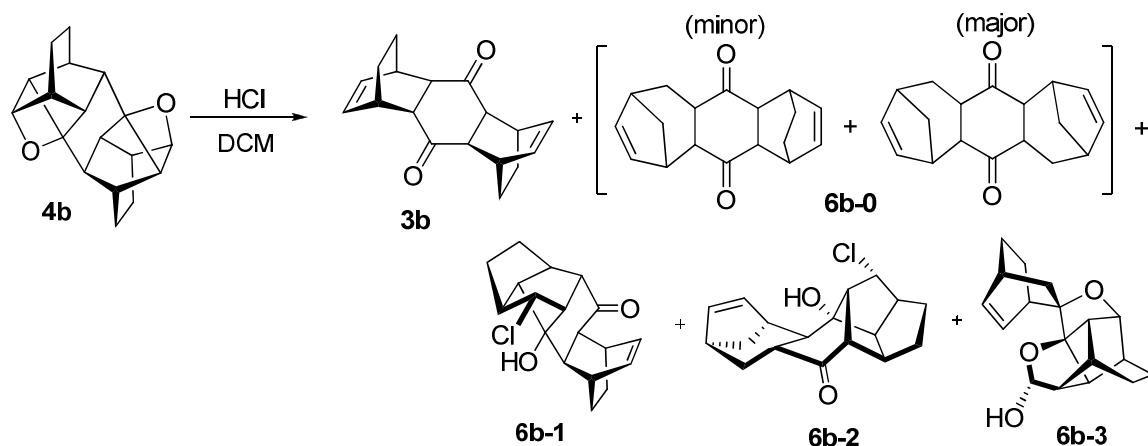


Figure 16. Experimental and predicted ^1H NMR spectra.

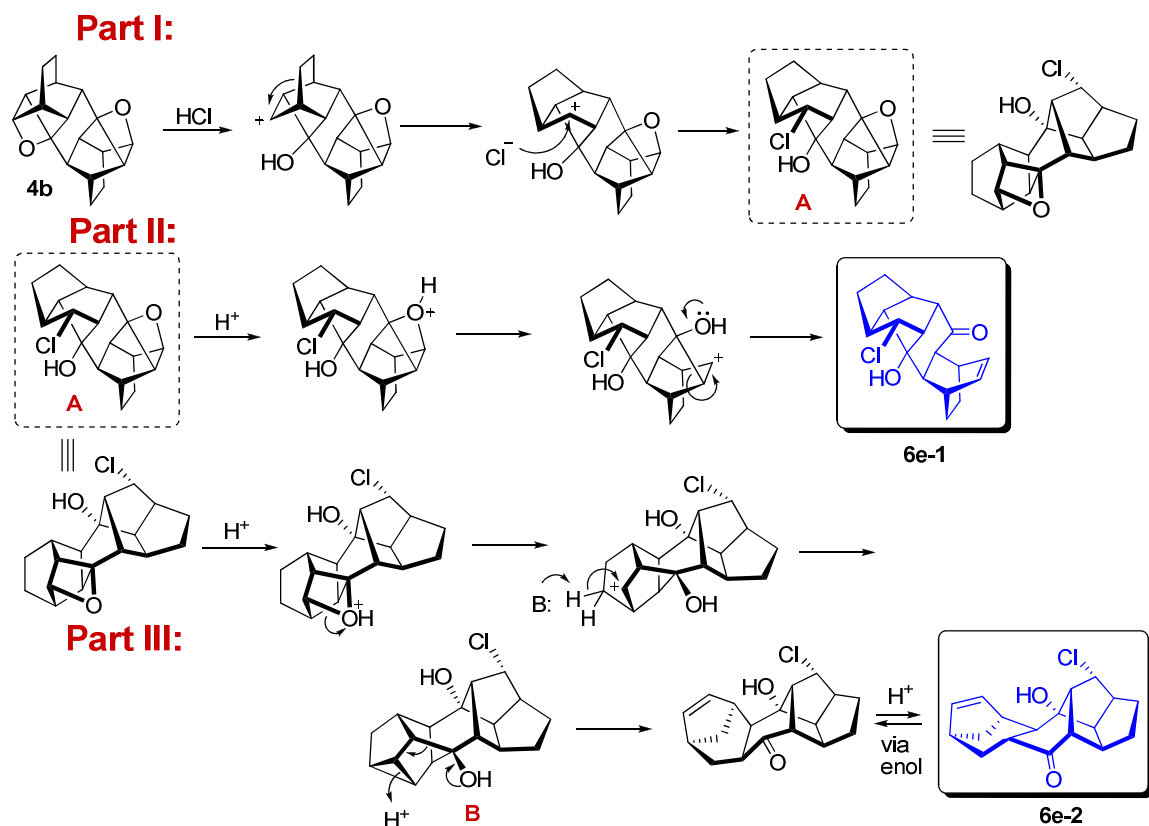
When *bis*-oxetane **4b** was treated with HCl in DCM, the isolated products turned out to be quite surprising. Unlike oxetanes **2**, *bis*-oxetane **4b** underwent several competing rearrangements. The major products are starting material **3b** and two isomeric dienes **6b-0**. The structures of **6b-0** were tentatively assigned based on the NMR data and by analogy with the X-ray structure of chlorohydrin **6b-2**. Two other products (**6b-1** and

6b-2) contained a chlorine atom and somewhat resembled what we observed in case of **2e** previously mentioned (Scheme 32). Compound **6b-3**, which was obtained and characterized by Teresa Arisco, was formed as a result of quite an unusual rearrangement, leading to the incorporation of a spiro connection into the scaffold (Scheme 35). The yields of products **6b-1**, **6b-2** and **6b-3** never exceeded 10%.



Scheme 35. Protolytic transformations of *bis*-oxetane **4b**.

A plausible mechanism for the formation of **6b-1** and **6b-2** involves protolytic cycloreversion to the *mono*-oxetane **A** (Scheme 36, Part I), occurring through 1,2-alkyl migration and nucleophilic attack similar to the ring opening of “6-6” oxetane **2e** (for references see Scheme 32). Intermediate **A** can undergo the *retro-P.-B.* reaction yielding product **6b-1** (Scheme 36, Part II). We suggested that cyclopropane **B** is the key intermediate in the formation of chlorohydrine **6b-2** (Scheme 36, Part III). Acid-catalyzed cyclopropyl ring opening in **B** followed by the *Grob* fragmentation gives *cis*-fused alkene, which equilibrates via enol into **6b-2**. All structures (**6b-1**, **6b-2** and **6b-3**) were confirmed by X-ray crystallography.



Scheme 36. A plausible mechanism for the formation of **6b-1** and **6b-2** from **4b**.

These results have elucidated how two simple steps - synthesizing the adducts and irradiating them to get various oxetanes - can offer expeditious access to highly complex aliphatic scaffolds from very simple and inexpensive starting materials. The first two steps are relatively clean and require very simple purification in some cases and often no purification at all. In case of *bis*-oxetane **4b**, the ring opening produced several products, requiring delicate separation.

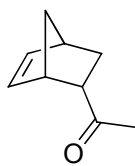
C. Experimental section.

Common solvents were purchased from Pharmco and used as is, except for THF, which was refluxed over and distilled from potassium benzophenone ketyl prior to use.

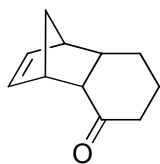
Common reagents were purchased from Aldrich or TCI America and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz or Varian Mercury 400 MHz instrument in CDCl₃ with TMS as an internal standard (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument (see Appendix C). High resolution mass spectra were obtained on the *MDS SCIEX/Applied Biosystems API QSTARTM Pulsar i Hybrid LC/MS/MS System* mass spectrometer by Dr. Shuji Kato from the University of Colorado at Boulder.

1. Preparation of the *Diels-Alder* adducts (1 and 3):

A solution of dienophile (1.0 eq) and diene (2.0-5.0 eq) in 5-10 mL of 1,2-dichlorobenzene (or xylenes) was heated in a bomb at 170-210°C for 24-72 h. After the reaction was cooled to room temperature, the solvent was removed on a high vacuum pump. The crude reaction mixture was purified on a silica gel column using a mixture of hexane and EtOAc as an eluent.

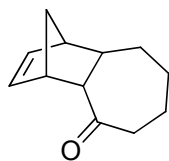


2-Acetyl-5-norbornene (mixture of the *endo*- and *exo*-isomers) (**1a**): Was purchased from Aldrich.



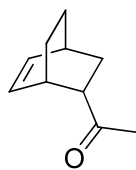
endo-Tricyclo[6.2.1.0^{2,7}]undec-9-ene-3-one (**1b**): from 3.0 g of 2-cyclohexen-1-one (31.2 mmol) and 5.2 g of 1,3-cyclopentadiene (78.0 mmol) at 170°C

(hexane/EtOAc gradient 30:1→20:1): 2.0 g (39%, *endo:exo* = 3:1 by NMR). ¹H NMR (400 MHz, CDCl₃) δ = 6.13 (dd, *J* = 5.7, 2.9 Hz, 1H), 5.97 (dd, *J* = 5.6, 3.0 Hz, 1H), 3.22 (m, 1H), 2.83 (m, 1H), 2.70-2.60 (m, 2H), 2.31-2.24 (dddddd, *J* = 18.5, 6.1, 2.7, 1.6, 0.8, 0.8 Hz, 1H), 1.96-1.84 (m, 2H), 1.79-1.62 (m, 2H), 1.40 (ddd, *J* = 8.3, 1.9, 1.9 Hz, 1H), 1.26 (d, *J* = 8.3 Hz, 1H), 0.72 (dddd, *J* = 12.8, 12.8, 11.0, 3.2 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 215.57, 137.83, 135.11, 51.84, 48.53, 46.73, 45.39, 41.59, 39.57, 28.19, 22.00.



***endo*-Tricyclo[7.2.1.0^{2,8}]dodec-10-ene-3-one (1c):** from 0.5 g of 2-

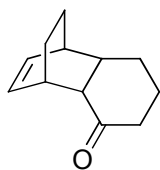
cyclohepten-1-one (4.54 mmol) and 1.2 g of 1,3-cyclopentadiene (18.2 mmol) at 170°C (hexane/EtOAc gradient 30:1→20:1): 0.17 g (21%, *endo:exo* = 2:1 by NMR). ¹H NMR (400 MHz, CDCl₃) δ = 6.36 (dd, *J* = 5.6, 2.9 Hz, 1H), 5.89 (dd, *J* = 5.6, 3.0 Hz, 1H), 3.15 (dd, *J* = 10.2, 3.3 Hz, 1H), 2.97 (m, 1H), 2.67 (m, 1H), 2.46-2.37 (m, 2H), 2.18 (ddd, *J* = 15.5, 10.6, 2.7 Hz, 1H), 1.93-1.84 (m, 1H), 1.75-1.69 (m, 1H), 1.67-1.44 (m, 3H), 1.40 (ddd, *J* = 8.3, 1.8, 1.8 Hz, 1H), 1.28 (dd, *J* = 8.3 Hz, 1H), 0.72 (dddd, *J* = 14.3, 12.6, 11.7, 4.5 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 213.81, 137.72, 132.50, 58.47, 48.76, 48.02, 45.04, 42.85, 41.70, 30.63, 27.46, 23.10.



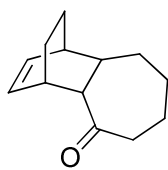
***endo*-6-Acetylbicyclo[2.2.2]oct-2-ene (1d):** from 0.84 g of methyl vinyl

ketone (12.0 mmol) and 1.44 g of 1,3-cyclohexadiene (18.0 mmol) at 160°C for 48 h (hexane/EtOAc gradient 40:1→30:1): 0.68 g (38%, *endo:exo* = 6:1 by NMR). ¹H NMR

(500 MHz, CDCl₃) δ = 6.26 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 6.08 (ddd, J = 7.8, 6.8, 1.2 Hz, 1H), 2.88 (m, 1H), 2.64 (ddd, J = 8.7, 6.6, 2.1 Hz, 1H), 2.58 (m, 1H), 2.09 (s, 3H), 1.63 (m, 2H), 1.61-1.55 (m, 1H), 1.51-1.45 (m, 1H), 1.30 (dddd, J = 12.0, 12.0, 3.6, 3.6 Hz, 1H), 1.26-1.21 (m, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 210.05, 135.40, 131.24, 51.76, 32.29, 29.76, 28.87, 28.53, 26.07, 24.72.



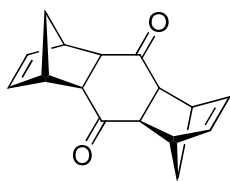
endo-Tricyclo[6.2.2.0^{2,7}]dodec-9-ene-3-one (1e): from 2.0 g of 2-cyclohexen-1-one (20.8 mmol) and 3.3 g of 1,3-cyclohexadiene (41.6 mmol) at 200°C (hexane/EtOAc gradient 30:1→20:1): 1.1 g (30%). ¹H NMR (400 MHz, CDCl₃) δ = 6.23 (t, J = 7.3 Hz, 1H), 6.10 (t, J = 7.3 Hz, 1H), 3.06 (m, 1H), 2.51 (dd, J = 10.8, 2.5 Hz, 1H), 2.44 (m, 1H) overlaps with 2.38 (m, 1H) overlaps with 2.33 (m, 1H), 2.07 (dddd, J = 18.4, 10.6, 7.4, 1.0 Hz, 1H), 1.79-1.70 (m, 3H), 1.58-1.45 (m, 2H), 1.26 (m, 2H), 0.98-0.87 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 214.74, 134.63, 133.25, 53.12, 42.41, 38.95, 36.02, 31.34, 29.80, 26.15, 24.17, 20.99.



endo-Tricyclo[7.2.2.0^{2,8}]tridec-10-ene-3-one (1f): from 1.0 g of 2-cyclohepten-1-one (9.1 mmol) and 1.5 g of 1,3-cyclohexadiene (18.2 mmol) at 200°C for 48 h (hexane/EtOAc 40:1): 0.17 g (10%). ¹H NMR (500 MHz, CDCl₃) δ = 6.33 (t, J = 7.3 Hz, 1H), 5.99 (t, J = 7.3 Hz, 1H), 2.91 (dd, J = 10.6, 1.4 Hz, 1H), 2.73 (m, 1H), 2.38-2.30 (m, 2H), 2.23 (ddd, J = 14.4, 10.0, 3.0 Hz, 1H), 2.09 (dddd, J = 12.5, 10.5, 2.0, 2.0 Hz, 1H), 1.88-1.80 (m, 1H), 1.67-1.60 (m, 1H), 1.57-1.36 (m, 5H), 1.24 (dddd, J = 12.0,

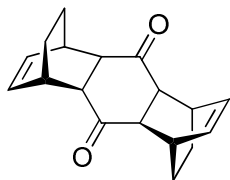
12.0, 3.4, 3.4 Hz, 1H), overlaps with 1.17 (dddd, $J = 11.7, 11.7, 4.3, 3.1$ Hz, 1H), 0.93 (dddd, $J = 14.6, 11.8, 11.8, 3.8$ Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) $\delta = 213.35, 134.58, 130.65, 57.94, 43.52, 41.99, 38.30, 33.24, 31.27, 28.43, 25.66, 24.35, 23.84$.

A solution of 1,4-benzoquinone (1.0 eq) and diene (2.0 eq) in 1,2-dichlorobenzene or DCM was heated in a bomb at 170-200°C for 24 h (or stirred at room temperature in DCM overnight). After the reaction was cooled to room temperature, the solvent was removed on a high vacuum pump. The crude reaction mixture was used either without further purification or was recrystallized.



1S(R), 2R(S), 4R(S), 5S(R), 8R(S), 9S(R), 11S(R), 12R(S)-

Pentacyclo[10.2.1.1^{5,8}.0^{2,11}.0^{4,9}]hexadeca-6,13-diene-3,10-dione (3a): from 4.0 g of 1,4-benzoquinone (37.0 mmol) and 6.1 g of 1,3-cyclopentadiene (92.5 mmol) in 30 mL of DCM for 24 h: 8.9 g (100%). ^1H NMR (500 MHz, CDCl_3) $\delta = 6.16$ (dd, $J = 1.8, 1.88$ Hz, 4H), 3.33 (m, 4H), 2.84 (m, 4H), 1.43 (ddd, $J = 1.8, 1.8, 8.6$ Hz, 2H), 1.26 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 212.85, 136.57, 53.41, 49.78, 48.45$.



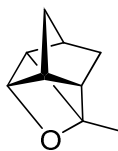
1S(R), 2R(S), 4R(S), 5S(R), 8R(S), 9S(R), 11S(R), 12R(S)-

Pentacyclo[10.2.2.2^{5,8}.0^{2,11}.0^{4,9}]octadeca-6,13-diene-3,10-dione (3b): from 2.0 g of 1,4-benzoquinone (18.5 mmol) and 3.0 g of 1,3-cyclohexadiene (37.0 mmol) in 15 mL of 1,2-dichlorobenzene for 24 h (recrystallized from hot CH_3CN): 3.9 g (79%). ^1H NMR

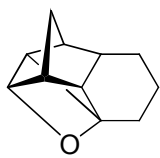
(400 MHz, CDCl₃) δ = 6.30 (m, 4H), 2.96 (m, 4H), 2.76 (m, 4H), 1.55-1.48 (m, 4H), 1.30-1.25 (m, 4H). ¹³C NMR (400 MHz, CDCl₃) δ = 210.85, 134.00, 53.78, 32.60, 24.66.

2. Preparation of the *Paternò-Büchi* adducts (**2** and **4**):

Approximately 3-10 mM solution of a precursor **1** in CH₃CN (or benzene) was irradiated in quartz reaction vessels in a Rayonet reactor equipped with RPR-3000 UV lamps (broadband 250-350 nm UV source with peak emission at 300 nm) for 24-72 hours. Irradiation resulted in a nearly quantitative conversion to **2** (70-90% by NMR), which were used without further purification. NOTE: We attempted to further purify reaction mixtures by chromatography. The strained polycyclic oxetanes **2** are not stable on silica gel, producing various amounts of rearranged products. To avoid this complication to some extent in some cases we passed 2 mL of pyridine through the column before column purification (hexane:EtOAc, 20:1→5:1).



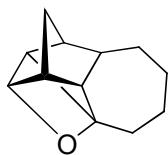
4-Methyl-3-oxatetracyclo[4.2.1.0^{2,5}.0^{4,8}]nonane (2a): from 300 mg of **1a** (2.2 mmol) in 600 mL of benzene, irradiation for 24 h: (> 80% by NMR of initial *endo*-2-acetyl-5-norbornene). ¹H NMR (500 MHz, CDCl₃) δ = 4.61 (dd, J = 3.6, 2.3 Hz, 1H), 2.78 (dddd, J = 3.7, 3.7, 1.8, 1.8 Hz, 1H), 2.65 (m, 1H), 2.23 (m, 1H), 1.97 (m, 1H), 1.73 (ddd, J = 10.6, 2.4, 2.4 Hz, 1H), 1.60 (ddd, J = 10.5, 2.3, 2.3 Hz, 1H), 1.57-1.51 (m, 2H), 1.44 (s, 3H).



2-Oxapentacyclo[6.4.0.0^{1,4}.0^{3,7}.0^{5,9}]dodecane (2b): from 200 mg of **1b**

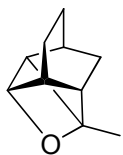
(1.23 mmol) in 525 mL of benzene (or CH₃CN), irradiation for 48 h: (> 80% by NMR).

¹H NMR (500 MHz, CDCl₃) δ = 4.73 (dd, *J* = 3.5, 2.3 Hz, 1H), 2.72 (m, 1H), 2.61 (m, 1H), 2.23 (ddd, *J* = 2.9, 2.9, 2.9 Hz, 1H), 2.01-1.95 (m, 2H), 1.88 (ddd, *J* = 11.9, 11.9, 4.8 Hz, 1H) overlaps with 1.84 (m, 1H), 1.75-1.67 (m, 2H), 1.67-1.59 (m, 2H), 1.56 (dddd, *J* = 14.2, 14.2, 6.0, 3.1 Hz, 1H), 1.42-1.35 (m, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 99.73, 88.03, 55.74, 53.73, 47.02, 43.57, 41.55, 39.86, 29.23, 26.36, 20.36.



2-Oxapentacyclo[6.5.0.0^{1,4}.0^{3,7}.0^{5,9}]tridecane (2c): from 170 mg of **1c**

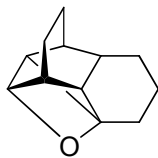
(1.06 mmol) in 30 mL of CH₃CN, irradiation for 24 h: (**2c** rearranged mostly into **5c** while being irradiated and on the column).



4-Methyl-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2d): from 300 mg of **1d**

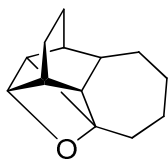
(2.00 mmol) in 700 mL of benzene, irradiation for 18 h: (> 88% by NMR). ¹H NMR (500 MHz, CDCl₃) δ = 4.37 (dd, *J* = 3.4, 2.1 Hz, 1H), 2.82 (dddd, *J* = 5.6, 3.6, 1.8, 1.8 Hz, 1H), 2.36 (m, 1H), 2.05 (d, *J* = 6.7 Hz, 1H), 1.86 (dddd, *J* = 13.9, 10.0, 10.0, 2.0 Hz, 1H), 1.78 (m, 1H), 1.67 (ddd, *J* = 9.5, 9.5, 4.0 Hz, 1H) overlaps with 1.66-1.63 (m, 2H), 1.52 (ddd, *J* = 13.4, 9.7, 4.6 Hz, 1H) overlaps with 1.49 (s, 3H), 1.09 (m, 1H). ¹³C NMR

(500 MHz, CDCl₃) δ = 97.64, 82.50, 56.86, 44.87, 39.49, 32.95, 28.57, 24.50, 17.52 overlaps with 17.52.



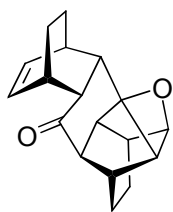
2-Oxapentacyclo[7.4.0.0^{1,4}.0^{3,8}.0^{5,10}]tridecane (2e): from 1.0 g of **1e** (5.67

mmol) in 0.5 L of CH₃CN, irradiation for 48 h: (> 95% by NMR). ¹H NMR (400 MHz, CDCl₃) δ = 4.40 (dd, J = 3.7, 1.8 Hz, 1H), 2.69 (dddd, J = 5.6, 3.6, 1.8, 1.8 Hz, 1H), 2.39 (m, 1H), 2.09 (m, 1H), 2.00-1.95 (m, 1H), 1.90 (ddd, J = 11.5, 11.5, 5.0 Hz, 1H), 1.82 (m, 1H) overlaps with 1.85-1.76 (dddd, J = 13.8, 10.0, 10.0, 2.3 Hz, 1H), 1.68 (m, 1H), 1.62 (m, 2H), 1.54-1.47 (m, 2H), 1.44-1.32 (m, 2H), 1.14 (dddd, J = 12.6, 10.0, 10.0, 1.8 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 98.58, 83.89, 54.59, 48.24, 44.67, 39.87, 34.77, 29.31, 29.29, 24.54, 20.46, 17.77.

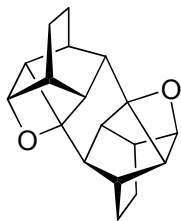


2-Oxapentacyclo[7.5.0.0^{1,4}.0^{3,8}.0^{5,10}]tetradecane (2f): from 120 mg of **1f**

(0.63 mmol) in 80 mL of CH₃CN, irradiation for 72 h: (> 65% by NMR, **2f** rearranged partially into **5f** while being irradiated). ¹H NMR (500 MHz, CDCl₃) δ = 4.26 (dd, J = 3.4, 2.1 Hz, 1H), 2.76 (dddd, J = 5.6, 3.7, 1.8, 1.8 Hz, 1H), 2.39 (m, 1H), 2.20-2.13 (m, 3H), 1.94 (dddd, J = 14.2, 6.4, 2.2, 1.1 Hz, 1H), 1.85 (dddd, J = 14.0, 9.7, 9.7, 2.0 Hz, 1H), 1.73 (ddd, J = 14.3, 7.3, 7.3 Hz, 1H), 1.67-1.63 (m, 1H) overlaps with HOD and 1.63-1.53 (m, 3H), 1.48 (m, 1H), 1.38-1.23 (m, 2H), 1.13 (dddd, J = 12.5, 9.6, 9.6, 1.2 Hz, 1H) overlaps with 1.07 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 101.10, 81.73, 58.71, 46.76, 45.57, 42.49, 34.61, 34.33, 33.30, 25.39, 25.17, 24.26, 17.98.



(**4b**^{*}): (formed as an intermediate). ¹H NMR (400 MHz, CDCl₃) δ = 6.32 (dd, J = 7.4, 7.4 Hz, 1H), 6.14 (dd, J = 7.2, 7.2 Hz, 1H), 4.56 (m, 1H), 3.22 (m, 1H), 2.83 (m, 2H), 2.68 (d, J = 9.5 Hz, 1H), 2.56 (dd, J = 9.5, 3.4 Hz, 1H), 2.51 (m, 1H) overlaps with 2.50 (m, 1H), 2.43 (m, 1H), 1.78 (m, 1H), 1.72 (m, 2H), 1.67-1.50 (m, 3H) overlaps with HOD, 1.33 (m, 1H), 1.27-1.12 (m, 2H). ¹³C NMR (400 MHz, CDCl₃) δ = 214.17, 135.16, 133.45, 97.12, 83.87, 59.33, 55.36, 50.37, 41.40, 39.77, 38.25, 34.22, 33.87, 29.35, 26.88, 24.05, 22.77, 17.17.



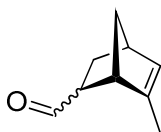
(**4b**): From 300 mg of **3b** (1.12 mmol) in 600 mL of CH₃CN, irradiation for 48 h: (> 95% by NMR). ¹H NMR (400 MHz, CDCl₃) δ = 4.39 (m, 1H), 2.86 (dddd, J = 5.5, 3.6, 1.8, 1.8 Hz, 1H), 2.43 (d, J = 2.1 Hz, 1H), 2.38 (m, 1H), 2.17-2.14 (m, 1H) overlaps with 2.13 (dddd, J = 7.8, 4.1, 2.0, 2.0 Hz, 1H), 1.84 (dddd, J = 13.9, 10.1, 10.1, 2.3 Hz, 1H), 1.70 (ddd, J = 3.7, 10.0, 13.7 Hz, 1H), 1.59 (ddd, J = 13.3, 9.7, 4.0 Hz, 1H), 1.18 (dddd, J = 13.1, 10.0, 10.0, 1.9 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 99.74, 83.59, 54.84, 46.02, 44.47, 38.38, 34.83, 23.21, 17.80.

3. Preparation of the rearranged products (5 and 6):

(A) **HCl-catalyzed formation of the rearranged adducts:** To a solution of oxetane 2 or 4b in DCM, HCl (4.0 M solution in dioxane) was added. The resulting

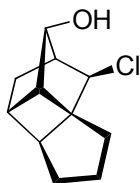
mixture was stirred at room temperature for 24 h, DCM was removed on a high-vacuum pump, then purified on a silica gel column using hexane–ethyl acetate (or hexane–ethanol).

(B) Rawal's conditions [27].



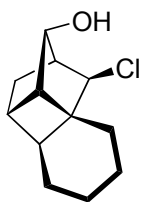
2-Methylbicyclo[2.2.1]hept-2-ene-6-carboxaldehyde (5a): (method A)

from 100 mL (3.7 mM) in benzene of **2a** (0.37 mmol) and 0.3 mL of HCl (1.20 mmol) (hexane/EtOAc 40:1): (all the attempts to purify a mixture of epimerized aldehydes failed).



2-Chlorotetracyclo[6.2.1.0^{3,7}.0^{3,9}]undecan-10-ol (5b): (method A) from 200

mg of **2b** (1.23 mmol) and 0.62 mL of HCl (2.47 mmol) in DCM (hexane/EtOAc 30:1→10:1): (> 90% by NMR). ¹H NMR (500 MHz, CDCl₃) δ = 4.37 (s, 1H), 4.05 (d, *J* = 10.6 Hz, 1H), 2.81 (d, *J* = 10.6 Hz, OH), 2.72 (m, 1H), 2.59 (ddd, *J* = 4.0, 1.9, 1.9 Hz, 1H), 2.08 (dd, *J* = 6.9, 4.1 Hz, 1H) overlaps with 2.06 (m, 1H), 1.94-1.72 (m, 7H), 1.44 (d, *J* = 12.7 Hz, 1H). ¹H NMR (500 MHz, CD₃OD) δ = 4.29 (s, 1H), 4.05 (s, 1H), 2.61 (m, 1H), 2.51 (ddd, *J* = 4.0, 1.9, 1.9 Hz, 1H), 2.08 (m, 1H) overlaps with 2.05 (dd, *J* = 6.9, 4.2 Hz, 1H), 1.93-1.87 (m, 3H), 1.85-1.73 (m, 4H), 1.47 (d, *J* = 12.6 Hz, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 83.44, 70.22, 60.68, 53.30, 48.81, 47.72, 35.43, 33.86, 33.12, 31.68, 26.57. ¹³C NMR (500 MHz, CD₃OD) δ = 83.27, 69.51, 62.30, 54.78, 51.03, 49.15 overlaps with CD₃OD, 36.36, 35.24, 34.02, 32.86, 27.73.



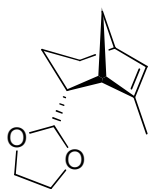
2-Chlorotetracyclo[7.2.1.0^{3,8}.0^{3,10}]dodecan-11-ol (5c): (method A) from

0.17 mg of **2c** (0.96 mmol) and 0.3 mL of HCl (1.20 mmol) in DCM (hexane/EtOAc 40:1→20:1): (> 90% by NMR). ¹H NMR (500 MHz, CDCl₃) δ = 4.28 (s, 1H), 4.11 (d, *J* = 10.0 Hz, 1H), 2.87 (m, 1H), 2.73 (m, 1H), 2.63 (d, *J* = 9.9 Hz, OH), 1.97 (m, 1H), 1.89 (dd, *J* = 7.1, 4.5 Hz, 1H), 1.84-1.79 (m, 2H) overlaps with 1.79 (ddd, *J* = 12.5, 7.2, 3.5 Hz, 1H), 1.63 (m, 1H), 1.53 (dd, *J* = 10.6, 7.5 Hz, 1H), 1.47 (dd, *J* = 12.5, 1.0 Hz, 1H), 1.42-1.35 (m, 2H), 1.27 (dddd, *J* = 13.7, 13.7, 10.6, 3.5 Hz, 1H), 1.06-0.97 (m, 1H). ¹H NMR (500 MHz, CD₃OD) δ = 4.13 (s, 1H), 4.06 (s, 1H), 2.77 (m, 1H), 2.57 (m, 1H), 1.92 (m, 1H), 1.81 (m, 2H), 1.72 (m, 2H), 1.59 (m, 1H), 1.51 (dd, *J* = 10.6, 7.5 Hz, 1H), 1.44 (dd, *J* = 12.4, 1.1 Hz, 1H), 1.38-1.22 (m, 3H), 1.01 (m, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 84.18, 75.04, 49.61 overlaps with 49.61, 47.89, 44.76, 36.27, 33.46, 30.07, 29.61, 24.06, 23.43. ¹³C NMR (500 MHz, CD₃OD) δ = 82.34, 72.73, 50.22, 49.47, 47.87 overlaps with CD₃OD, 44.29, 36.15, 32.91, 29.93, 28.96, 23.84, 23.30.



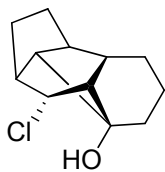
7-Methylbicyclo[3.2.1]oct-6-ene-2-carboxaldehyde (5d-1): (method A) from

34 mg of **2d** (0.23 mmol) and 0.1 mL of HCl (0.40 mmol) in DCM (hexane/EtOAc 40:1): (all the attempts to separate a mixture of epimerized aldehydes (*endo:exo* = 2.2:1) failed).



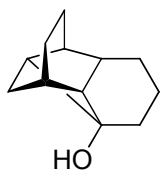
7-Methyl-endo-2-(1,3-dioxolan-2-yl)bicyclo[3.2.1]oct-6-ene (5d-2):

(method A) from 34 mg of **2d** (0.23 mmol) and 0.1 mL of HCl (0.40 mmol) in THF/ethylene glycol mixture (1:1) (hexane/EtOAc 40:1): (30 mg, 68%). ^1H NMR (500 MHz, CDCl_3) δ = 5.48 (s, 1H), 4.53 (d, J = 7.3 Hz, 1H), 3.98-3.91 (m, 2H), 3.88-3.81 (m, 2H), 2.47 (m, 2H), 2.10 (dddd, J = 10.2, 5.4, 5.4, 1.8 Hz, 1H), 1.81 (m, 3H), 1.69-1.61 (m, 2H), 1.45-1.38 (m, 2H), 1.36 (d, J = 9.8 Hz, 2H). ^{13}C NMR (500 MHz, CDCl_3) δ = 140.76, 127.41, 106.89, 64.78, 64.63, 46.41, 44.35, 41.59, 39.45, 24.48, 21.21, 17.37.



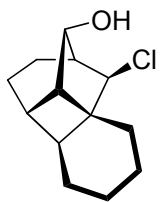
2-Chlorotetracyclo[7.2.1.0^{3,8}.0^{4,12}]dodecan-4-ol (5e-1): (method A) from

50 mg of **2e** (0.28 mmol) and 0.1 mL of HCl (0.40 mmol) in DCM (hexane/EtOAc 30:1→5:1, then hexane/EtOH 10:1→1:1): (20 mg, ~ 40%). ^1H NMR (400 MHz, CDCl_3) δ = 3.47 (d, J = 2.4 Hz, 1H), 2.89 (m, 1H), 2.64 (s, 1OH), 2.15-2.10 (m, 2H) overlaps with 2.10-2.01 (m, 1H), 1.94 (dd, J = 13.4, 6.5 Hz, 1H), 1.85-1.68 (m, 4H), 1.68-1.56 (m, 3H) overlaps with HOD, 1.45 (dd, J = 13.3, 8.1 Hz, 1H) overlaps with 1.44-1.39 (m, 2H). ^1H NMR (400 MHz, CD_3OD) δ = 3.39 (d, J = 2.6 Hz, 1H), 2.87 (m, 1H), 2.17 (dd, J = 8.1, 5.5 Hz, 1H), 2.11-2.02 (m, 2H), 1.90-1.85 (m, 1H), 1.83-1.73 (m, 3H), 1.66 (m, 1H), 1.63-1.55 (m, 3H), 1.53-1.42 (m, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ = 87.91, 67.57, 56.40, 55.92, 54.87, 47.96, 37.89, 32.91, 32.48, 29.09, 28.71, 18.98. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{17}\text{ClNaO}^+$ (MNa^+) 235.0860, found 235.0857.



Tetracyclo[6.2.2.0^{2,7}.0^{3,9}]dodecan-3-ol (5e-2): (method B) from 0.5 g of **2e**

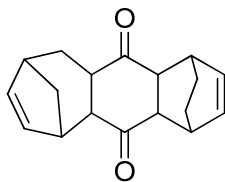
(2.84 mmol), 0.14 g of Li wire (20.17 mmol), 1.5 g of DBB (5.63 mmol) in THF at 0°C for 3 h, then 6.0 mL of Et₃Al (5.96 mmol) -78°C for 6 h (hexane/EtOAc 60:1→20:1): (0.48 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ = 2.18 (dddd, *J* = 10.9, 7.2, 1.9, 1.9 Hz, 1H), 2.11 (m, 1H), 1.94-1.88 (m, 1H), 1.87-1.81 (m, 3H), 1.79-1.70 (m, 2H), 1.69-1.63 (m, 1H), 1.60-1.49 (m, 5H), 1.47-1.40 (m, 2H), 1.31-1.22 (m, 2H). ¹³C NMR (400 MHz, CDCl₃) δ = 85.75, 49.95, 46.08, 39.44, 36.23, 34.92, 32.92, 29.97, 28.54, 25.17, 24.54, 19.97. HRMS (ESI) calcd for C₁₂H₁₈NaO⁺ (MNa⁺) 201.1250, found 201.1254.



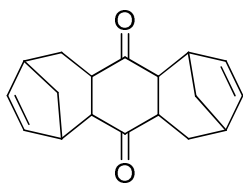
2-Chlorotetracyclo[7.2.2.0^{3,8}.0^{3,10}]tridecan-11-ol (5f): (method A) from 57

mg of **2f** (0.30 mmol) and 0.1 mL of HCl (0.40 mmol) in DCM (hexane/EtOAc 40:1→30:1): (> 90% by NMR). ¹H NMR (500 MHz, CDCl₃) δ = 4.19 (d, *J* = 9.5 Hz, 1H), 4.15 (s, 1H), 2.79 (m, 2H), 2.24 (d, *J* = 9.5 Hz, OH), 2.18 (ddd, *J* = 14.7, 9.3, 9.3 Hz, 1H), 2.07 (dddd, *J* = 6.6, 6.6, 2.3, 2.3 Hz, 1H), 2.02-1.95 (m, 1H), 1.87-1.83 (m, 1H), 1.78 (ddd, *J* = 14.6, 10.5, 8.8 Hz, 1H), 1.72-1.61 (m, 4H), 1.57-1.48 (m, 2H), 1.40-1.31 (m, 2H), 1.24-1.17 (m, 1H). ¹H NMR (500 MHz, CD₃OD) δ = 4.18 (s, 1H), 4.05 (s, 1H), 2.69 (d, *J* = 8.9 Hz, 1H), 2.62 (dd, *J* = 8.6, 2.3 Hz, 1H), 2.10 (ddd, *J* = 14.7, 9.2, 9.2 Hz, 1H), 2.01-1.94 (m, 2H), 1.82-1.74 (m, 2H), 1.67-1.50 (m, 5H), 1.50-1.41 (m, 1H), 1.38-1.27 (m, 2H), 1.23-1.14 (m, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 80.02, 78.37, 52.70,

48.35, 46.27, 40.82, 38.88, 30.29, 30.05, 27.69, 22.06, 20.97, 20.29. ^{13}C NMR (500 MHz, CD_3OD) δ = 79.84, 78.38, 54.39, 49.86, 47.16, 42.98, 40.36, 31.82, 31.02, 28.91, 23.47, 22.50, 21.53.

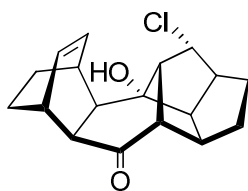


(6b-0 minor product): from 1.18 g of **11** (4.40 mmol) and 4.4 mL of HCl (17.6 mmol) in DCM for 10 min (hexane/EtOAc 10:1→1:1): (< 5% by NMR). ^1H NMR (500 MHz, CDCl_3) δ = 5.96 (dd, J = 5.7, 2.8 Hz, 1H), 5.77 (dd, J = 5.7, 2.5 Hz, 1H), 5.72 (dd, J = 5.7, 2.8 Hz, 1H), 5.66 (dd, J = 5.7, 2.7 Hz, 1H), 3.37 (ddd, J = 5.3, 2.6, 2.6 Hz, 1H), 3.16 (ddd, J = 5.3, 2.5, 2.5 Hz, 1H), 2.78 (ddd, J = 10.6, 8.7, 5.7 Hz, 1H) overlaps with 2.74 (dd, J = 7.6, 2.4 Hz, 1H), 2.71-2.67 (m, 2H), 3.66-2.55 (m, 2H), 2.09-2.04 (m, 1H) overlaps with 2.04 (dd, J = 14.3, 2.3 Hz, 1H) and overlaps with 2.03-1.98 (dddd, J = 10.6, 5.4, 5.4, 2.1 Hz, 1H), 1.67 (ddd, J = 13.6, 10.7, 2.4 Hz, 1H), 1.63 (m, 1H), 1.57-1.52 (m, 1H) overlaps with HOD, 1.46 (d, J = 10.3 Hz, 1H), 1.29 (d, J = 10.5 Hz, 1H). ^{13}C NMR (500 MHz, CDCl_3) δ = 212.55, 210.45, 138.89, 135.48, 131.43, 130.29, 48.56, 48.32, 44.70, 43.33, 43.31, 43.22, 41.53, 39.81, 38.19, 38.03, 25.43, 23.37.

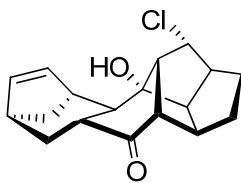


(6b-0 major product): (40-50% by NMR). ^1H NMR (500 MHz, CDCl_3) δ = 6.36 (ddd, J = 8.0, 6.7, 1.2 Hz, 1H), 6.18 (ddd, J = 7.7, 6.6, 1.2 Hz, 1H), 5.92 (dd, J = 5.7, 2.8 Hz, 1H), 5.85 (dd, J = 5.7, 2.8 Hz, 1H), 3.42 (m, 1H), 3.10 (ddd, J = 5.3, 2.6, 2.6 Hz, 1H), 2.95 (m, 1H) overlaps with 2.92 (dd, J = 10.3, 2.4 Hz, 1H), 2.69 (dd, J =

10.2, 2.4 Hz, 1H), 2.64 (dddd, $J = 5.6, 2.8, 2.8, 2.8$ Hz, 1H), 2.54 (ddd, $J = 14.9, 10.54, 5.9$ Hz, 1H), 2.06 (dd, $J = 14.8, 2.3$ Hz, 1H), 1.94 (dddd, $J = 10.6, 5.4, 5.4, 2.0$ Hz, 1H), 1.70 (ddd, $J = 13.5, 10.6, 2.5$ Hz, 1H), 1.64 (m, 1H), 1.56-1.48 (m, 2H), 1.37-1.26 (m, 2H), 1.20 (d, $J = 10.5$ Hz, 1H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 210.49, 210.44, 135.77, 134.89, 132.89, 130.84, 52.43, 51.91, 48.74, 43.27, 42.37, 38.53, 37.95, 36.25, 31.47, 25.48, 23.85, 23.70$.

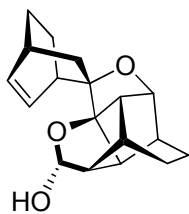


(6b-1): (< 10% by NMR). ^1H NMR (500 MHz, CDCl_3) $\delta = 6.30$ (ddd, $J = 8.2, 6.5, 1.3$ Hz, 1H), 6.24 (ddd, $J = 7.8, 6.4, 1.5$ Hz, 1H), 3.50 (d, $J = 2.2$ Hz, 1H), 3.26 (m, 2H), 2.94 (m, 1H), 2.79 (s, OH), 2.75 (dd, $J = 10.0, 3.0$ Hz, 1H), 2.62 (dd, $J = 10.2, 1.6$ Hz, 1H), 2.32 (ddd, $J = 4.6, 4.6, 1.3$ Hz, 1H), 2.12 (m, 2H), 2.05 (m, 1H), 1.81 (m, 2H), 1.77 (m, 1H), 1.58-1.53 (m, 3H) overlaps with HOD 1.31 (m, 2H).



(6b-2): (method A) from 1.18 g of **4b** (4.40 mmol) and 4.4 mL of HCl (17.6 mmol) in DCM for 10 min (hexane/EtOAc 10:1→1:1): (< 10% by NMR). ^1H NMR (400 MHz, CDCl_3) $\delta = 5.98$ (dd, $J = 5.8, 2.7$ Hz, 1H), 5.94 (dd, $J = 5.7, 2.7$ Hz, 1H), 3.59 (d, $J = 2.1$ Hz, 1H), 3.13 (ddd, $J = 5.3, 2.5, 2.5$ Hz, 1H), 2.85 (m, 1H), 2.80 (s, 1OH), 3.67 (m, 1H) overlaps with 2.66-2.61 (m, 1H), 2.32-2.29 (m, 2H), 2.15-2.06 (m, 2H), 2.02 (dddd, $J = 10.5, 5.4, 5.4, 2.1$ Hz, 1H), 1.91-1.85 (m, 2H), 1.82 (m, 1H), 1.63-1.55 (m, 3H), 1.29 (ddd, $J = 13.3, 11.0, 2.3$ Hz, 1H), 1.22 (d, $J = 10.3$ Hz, 1H). ^{13}C NMR

(400 MHz, CDCl₃) δ = 213.73, 133.94, 132.53, 87.57, 66.61, 59.43, 59.36, 52.37, 49.32, 44.95, 44.93, 42.72, 42.56, 40.27, 38.53, 32.18, 30.26, 23.71. HRMS (ESI) calcd for C₁₈H₂₁ClNaO₂⁺ (MNa⁺) 327.1122, found 327.1112.



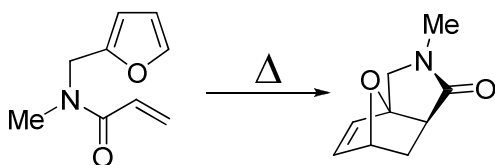
(6b-3): (< 10% by NMR). ¹H NMR (400 MHz, CDCl₃) δ = 6.39 (ddd, J = 8.0, 6.6, 1.2 Hz, 1H), 6.25 (ddd, J = 8.0, 6.5, 1.4 Hz, 1H), 5.25 (d, J = 4.9 Hz, 1H), 3.73 (d, J = 3.1 Hz, 1H), 2.68 (m, 1H), 2.63 (m, 1H), 2.54 (d, J = 5.4 Hz, 1H), 2.46 (m, 1H) overlaps with 2.42 (dddd, J = 6.3, 2.1, 2.1, 2.1 Hz, 1H), 2.17 (dddd, J = 12.5, 9.9, 4.5, 2.4 Hz, 1H) overlaps with 2.12 (d, J = 2.4 Hz, 1H), 2.04 (m, 1H), 1.96 (dd, J = 13.7, 1.8 Hz, 1H) overlaps with 1.94-1.91 (m, 1H), 1.65 (ddd, J = 13.7, 3.5, 3.5 Hz, 1H), 1.59-1.51 (m, 3H) overlaps with 1.51-1.38 (m, 2H), 1.17 (dddd, J = 11.9, 11.9, 4.3, 2.9, 2.9 Hz, 1H), 1.03 (dddd, J = 12.4, 12.4, 3.8, 3.8 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 134.47, 132.55, 101.76, 99.24, 79.64, 78.88, 48.46, 48.17, 43.13, 39.99, 38.84, 37.20, 32.70, 30.38, 25.24, 22.81, 22.13, 18.38. HRMS (ESI) calcd for C₁₈H₂₂NaO₃⁺ (MNa⁺) 309.1461, found 309.1459.

Chapter Five: Photoinduced transformations in the *Hetero-Diels-Alder* adducts

A. Introduction – Part I.

The *intramolecular Diels-Alder* (IMDA) reaction of furans with internal (built-in) dienophiles is an effective method for the generation of highly functionalized polycyclic systems, which are attractive starting scaffolds for diversity oriented synthesis [40]. IMDA reactions between inactivated furans and dienophiles take place generally faster and at lower temperature compared to their *intermolecular* counterparts.

When a furan is connected to a dienophile by a tether, the triene undergoes IMDA reaction with excellent stereocontrol to provide a tricyclic system [40a].



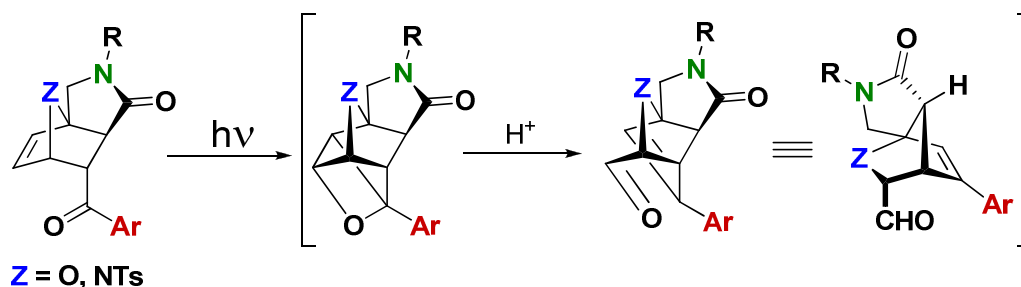
As an extension of this work, we decided to also examine the IMDA reaction utilizing pyrrole as a diene partner to prepare tricyclic molecules with a 7-azabicyclo[2.2.1]hept-2-ene moiety. Although there are plenty of examples of the *intermolecular Diels-Alder* cycloaddition reaction of *N*-protected pyrroles [41a-b], only a few

reports describing IMDA reaction cycloaddition of pyrrole have been published [41c].

This may be due to the aromatic character of the pyrrole ring.

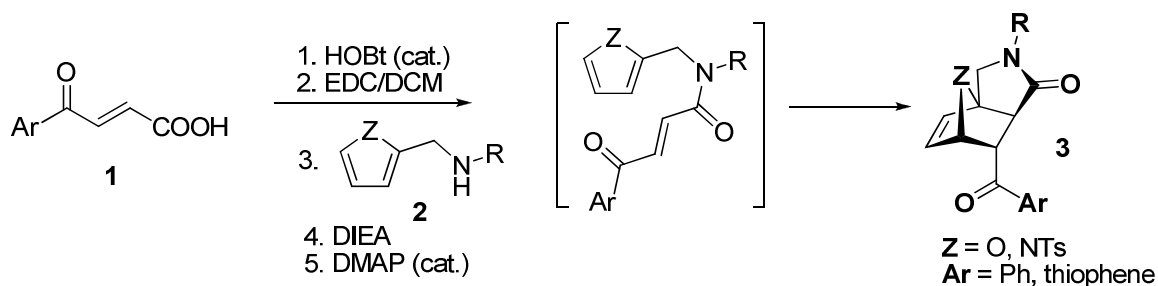
B. Results and discussion – Part I.

With this in mind we hypothesized that polycyclic *Hetero-Diels-Alder* (*H.-D.-A.*) adducts containing an *endo*-aroyl group could react via [2+2] photo-cycloaddition and further undergo oxametathesis when exposed to acidic media producing highly functionalized and unique scaffolds (Scheme 37):



Scheme 37: Oxametathesis of the hypothesized *Hetero-Paternò-Büchi* adducts.

To prove this concept we first synthesized various furan- and pyrrol-based amines **2**, which were further coupled with 4-oxobutenoic acid **1**. The resulting newly-formed conjugates immediately underwent IMDA cycloaddition to provide tricyclic compounds **3** with an aroyl group in the *endo*-position (Scheme 38):

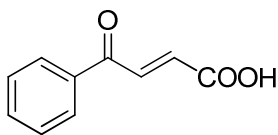


Scheme 38: Preparation of *Hetero-Diels-Alder* adducts **3**.

However, to our great disappointment, *H.-D.-A.* adducts **3** failed to undergo the *P.-B.* photocycloaddition. This could be due to the fact that a lactam's five-membered ring makes tricycle **3** very rigid, which precludes the *endo*-aroyl group from reaching the double bond and reacting to form the desired *P.-B.* adducts. Numerous computational predictions confirmed that as well.

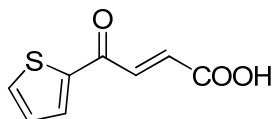
C. Experimental section – Part I.

1. Preparation of butenoic acids (1):



(2E)-4-oxo-4-phenylbut-2-enoic acid (*trans*-3-benzoylacrylic acid) (**1a**):

To a mixture of 100 mL of anhydrous, thiophene-free benzene and 5 g (51 mmol) of maleic anhydride at room temperature, there was added in small portions 13.75 g (103 mmol) of aluminum chloride. The temperature rose to 40-45°C during the addition and the mixture was then refluxed for 3-4 hours. The reaction mixture was decomposed with ice and 1:1 hydrochloric acid, the resulting mixture was then extracted with DCM and washed over anhydrous Na₂SO₄. The organic solvent was removed under reduced pressure to afford 7.2 g (80%) of pure acid [42]. ¹H NMR (500 MHz, CDCl₃) δ = 8.02 (d, *J* = 7.7 Hz, 2H) overlaps with 8.01 (d, *J* = 15.5 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 6.90 (d, *J* = 15.5 Hz, 1H).



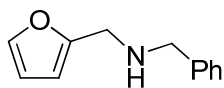
(2E)-4-oxo-4-(2-thienyl)but-2-enoic acid (**1b**):

A mixture of 3.5 mL (32.4 mmol) of 2-acetylthiophene and 3.0 g of glyoxalic acid monohydrate (32.3

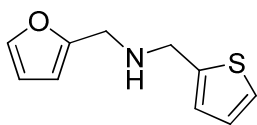
mmol) in 10 mL of glacial HOAc and 1 mL of conc. HCl was heated under reflux conditions for 8 h. The solvents were removed under reduced pressure, the residue was taken up in hexane/EtOAc/DCM/EtOH and the solid that formed was filtered and recrystallized [43]. ^1H NMR (500 MHz, CDCl_3) δ = 7.88 (dd, J = 3.9, 1.1 Hz, 1H), 7.86 (d, J = 15.4 Hz, 1H), 7.79 (dd, J = 4.9, 1.1 Hz, 1H), 7.22 (dd, J = 4.9, 3.9 Hz, 1H), 6.95 (d, J = 15.4 Hz, 1H).

2. Preparation of the amines (2):

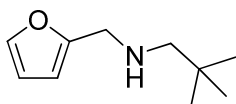
An aldehyde (1.0-1.1 eq) was added to a stirred solution of an amine (1.0 eq) in anhydrous ethanol at room temperature. After complete formation of the imine (3 hours), excess sodium borohydride (2.0-2.5 eq) was added in three portions at 10°C . After complete addition, the reaction mixture was stirred overnight and then diluted with water (100 mL), acidified with aq. HCl to pH 1 and extracted with DCM. The aqueous layer was adjusted to pH 10 with 5% of aq. NaOH and after that extracted with DCM. The combined DCM layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* [40b].



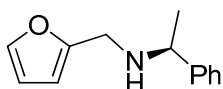
***N*-Benzyl-*N*-(2-furylmethyl)amine (2a):** from 2.85 mL of furfurylamine (32.3 mmol), 3.3 mL of benzaldehyde (32.4 mmol) and 2.5 g of NaBH_4 (66.1 mmol): 5.8 g (95%). ^1H NMR (500 MHz, CDCl_3) δ = 7.38 (dd, J = 1.8, 0.8 Hz, 1H), 7.34 (s, 2H), 7.33 (s, 2H), 7.26 (m, 1H) overlaps with CDCl_3 , 6.32 (dd, J = 3.2, 1.8 Hz, 1H), 6.19 (dd, J = 3.2, 0.8 Hz, 1H), 3.79 (s, 4H), 1.66 (br. s, NH).



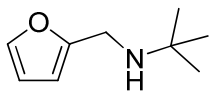
***N*-(2-Furylmethyl)-*N*-(2-thienylmethyl)amine (2b)**: from 1.0 mL of furfurylamine (11.3 mmol), 1.0 mL of 2-thiophenecarboxaldehyde (10.7 mmol) and 0.82 g of NaBH₄ (21.7 mmol): 2.0 g (97%). ¹H NMR (500 MHz, CDCl₃) δ = 7.38 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.23 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.96 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.93 (m, 1H), 6.33 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.19 (d, *J* = 3.1, 0.8 Hz, 1H), 3.98 (m, 2H), 3.82 (s, 2H), 1.69 (br. s, NH).



***N*-(2-Furylmethyl)-*N*-neopentylamine (2c)**: from 1.0 mL of furfurylamine (11.3 mmol), 1.1 mL of pivalaldehyde (10.1 mmol) and 1.0 g of NaBH₄ (26.4 mmol): 1.6 g (95%). ¹H NMR (500 MHz, CDCl₃) δ = 7.36 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.31 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.16 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.78 (s, 2H), 2.34 (s, 2H), 1.34 (br. s, NH), 0.90 (s, 9H).

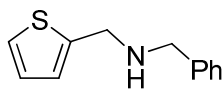


***N*-(2-Furylmethyl)-*N*-[(1*S*)-1-phenylethyl]amine (2d)**: from 2.0 mL of furfural (24.1 mmol), 3.1 mL of (*S*)-(-)-α-methylbenzylamine (24.0 mmol) and 2.3 g of NaBH₄ (60.8 mmol): 4.6 g (95%). ¹H NMR (500 MHz, CDCl₃) δ = 7.38 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.37 (m, 2H), 7.36 (s, 2H), 7.28 (m, 1H) overlaps with CDCl₃, 6.32 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.13 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.81 (q, *J* = 6.6 Hz, 1H), 3.69 (d, *J* = 14.5 Hz, 1H), 3.60 (d, *J* = 14.5 Hz, 1H), 1.72 (br. s, NH), 1.39 (d, *J* = 6.6 Hz, 3H).

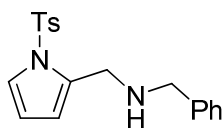


***N*-(*tert*-Butyl)-*N*-(2-furylmethyl)amine (2e)**: from 2.0 mL of furfural (24.1 mmol), 2.5 mL of *tert*-butylamine (23.8 mmol) and 2.3 g of NaBH₄ (60.8 mmol):

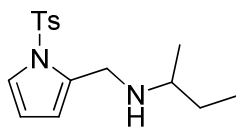
3.5 g (95%). ^1H NMR (500 MHz, CDCl_3) δ = 7.35 (dd, J = 1.8, 0.8 Hz, 1H), 6.30 (dd, J = 3.2, 1.8 Hz, 1H), 6.16 (dd, J = 3.2, 0.8 Hz, 1H), 3.76 (s, 2H), 1.16 (s, 9H), 1.09 (br. s, NH).



***N*-(Benzyl)-*N*-(2-thienylmethyl)amine (2f)**: from 2.0 mL of 2-thiophenecarboxaldehyde (21.4 mmol), 2.3 mL of benzylamine (21.1 mmol) and 2.3 g of NaBH_4 (60.8 mmol): 4.1 g (95%). ^1H NMR (500 MHz, CDCl_3) δ = 7.34 (m, 2H), 7.33 (m, 2H), 7.27 (m, 1H) overlaps with CDCl_3 , 7.22 (dd, J = 5.0, 1.2 Hz, 1H), 6.96 (dd, J = 5.0, 3.4 Hz, 1H), 6.93 (m, 1H), 4.00 (m, 2H), 3.84 (s, 2H), 1.70 (br. s, NH).

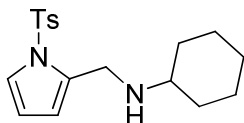


***N*-Benzyl-*N*-{[1-(*p*-toluenesulfonyl)-1H-pyrrol-2-yl]methyl}amine (2g)**: from 0.5 g of 1-(*p*-toluenesulfonyl)pyrrole-2-aldehyde (2.0 mmol), 0.25 mL of benzylamine (2.3 mmol) and 0.2 g of NaBH_4 (5.3 mmol): 0.65 g (95%). ^1H NMR (500 MHz, CDCl_3) δ = 7.63 (d, J = 8.4 Hz, 2H), 7.33-7.26 (m, 5H) overlaps with CDCl_3 and 7.26-7.22 (m, 3H), 6.23 (t, J = 3.3 Hz, 1H), 6.17 (m, 1H), 3.80 (s, 2H), 3.70 (s, 2H), 2.38 (s, 3H), 1.80 (br. s, NH).



***N*-(1-Methylpropyl)-*N*-{[1-(*p*-toluenesulfonyl)-1H-pyrrol-2-yl]methyl}amine (2h)**: from 1.0 g of 1-(*p*-toluenesulfonyl)pyrrole-2-aldehyde (4.0 mmol), 0.4 mL of *sec*-butylamine (4.0 mmol) and 0.38 g of NaBH_4 (10.0 mmol): 1.16 g (95%). ^1H NMR (500 MHz, CDCl_3) δ = 7.68 (d, J = 8.4 Hz, 2H), 7.30-7.27 (m, 3H), 6.22 (t, J = 3.3 Hz, 1H), 6.15 (m, 1H), 3.82 (d, J = 14.9 Hz, 1H), 3.75 (d, J = 14.9 Hz, 1H),

2.49 (m, 1H), 2.40 (s, 3H), 1.66 (br. s, NH), 1.42 (m, 1H), 1.28 (m, 1H), 0.98 (d, $J = 6.3$ Hz, 3H), 0.85 (t, $J = 7.5$ Hz, 3H).



***N*-Cyclohexyl-*N*-{[1-(*p*-toluenesulfonyl)-1H-pyrrol-2-**

yl]methyl}amine (2i): from 1.0 g of 1-(*p*-toluenesulfonyl)pyrrole-2-aldehyde (4.0 mmol), 0.5 mL of cyclohexylamine (4.4 mmol) and 0.38 g of NaBH₄ (10.0 mmol): 1.26 g (95%). ¹H NMR (500 MHz, CDCl₃) δ = 7.68 (d, $J = 8.4$ Hz, 2H), 7.30-2.27 (m, 3H), 6.22 (t, $J = 3.3$ Hz, 1H), 6.15 (m, 1H), 3.81 (s, 2H), 2.40 (s, 3H), 2.36 (dddd, $J = 10.5, 10.5, 3.8, 3.8$ Hz, 1H), 1.77 (m, 2H), 1.73-1.64 (m, 2H) overlaps with 1.66 (br. s, NH), 1.59 (m, 1H), 1.24-1.12 (m, 3H), 1.04 (m, 2H).

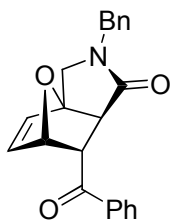
3. Preparation of the *Diels-Alder* adducts (3):

(A) To a solution of dienophile acid **1** (1 eq) in DCM was added EDC or DIC (0.5 eq) and HOBT (cat.), the mixture was stirred at room temperature for 45 min. The amine **2** was added to the solution of the solution of pre-activated acid (0.5 eq) in DCM and then DIEA (1 eq) and DMAP (cat.) were added to the reaction mixture. After the amine was consumed, the reaction mixture was diluted with DCM and washed with NaOH (5%), aqueous HCl (5%) and brine. The organic layer was dried, filtered, and evaporated to give the crude compound, which was purified by silica gel chromatography (eluted with hexane/EtOAc = 20:1→4:1) [40a, 41].

(B) The amine **2** (1.0 eq) was dissolved in THF or ether, the solution was cooled to -78^oC. Acryloyl chloride (1.2 eq) was then added and the resulting mixture was stirred for 10-20 min at -78^oC to room temperature. The reaction mixture was washed with H₂O

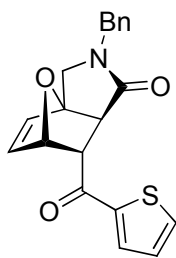
x 2 (50 mL) and extracted with DCM. The organic layer was dried over anhydrous NaSO₄. The crude product was purified by silica gel chromatography (eluted with hexane/EtOH = 30:1→10:1).

All the X-ray structures can be found in Appendix D.



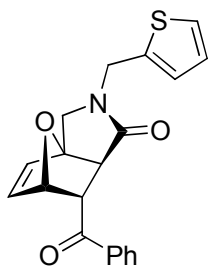
endo-6-Benzoyl-3-benzyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-

ene (3a-1): from 1.00 g of (2E)-4-oxo-4-phenylbut-2-enoic acid (**1a**) (5.68 mmol), 0.44 mL of DIC (2.84 mmol), 0.53 g of *N*-benzyl-*N*-(2-furylmethyl)amine (**2a**) (2.83 mmol) and 1.0 mL of DIEA (5.74 mmol) (hexane/EtOAc gradient 4:1→2:1): 0.63 g (65%). ¹H NMR (500 MHz, CDCl₃) δ = 8.26 (d, *J* = 7.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.31-7.26 (m, 3H), 6.45 (d, *J* = 5.8 Hz, 1H), 6.36 (dd, *J* = 5.8, 1.6 Hz, 1H), 5.34 (dd, *J* = 4.5, 1.6 Hz, 1H), 4.61 (d, *J* = 14.9 Hz, 1H), 4.55 (d, *J* = 14.9 Hz, 1H), 4.36 (dd, *J* = 4.5, 3.9 Hz, 1H), 3.87 (d, *J* = 11.9 Hz, 1H), 3.59 (d, *J* = 11.9 Hz, 1H), 3.09 (d, *J* = 3.9 Hz, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 196.99, 173.04, 136.10, 136.08, 135.87, 133.61 (two overlapping peaks), 128.92, 128.83, 128.80, 127.92, 127.71, 90.62, 81.40, 51.57, 51.45, 48.78, 46.75. HRMS (ESI) calcd for C₂₂H₁₉NNaO₃⁺ (MNa⁺) 368.1257, found 368.1269.



3-Benzyl-endo-6-thienoyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-

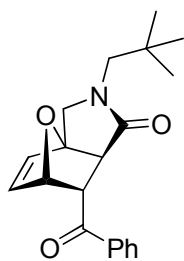
ene (3a-2): from 1.39 g of (2E)-4-oxo-4-(2-thienyl)but-2-enoic acid (**1b**) (7.63 mmol), 0.73 g of EDC (3.81 mmol), 0.71 g of **2a** (3.79 mmol) and 1.33 mL of DIEA (7.64 mmol) (hexane/EtOAc gradient 20:1→2:1): 0.47 g (35%). ¹H NMR (500 MHz, CDCl₃) δ = 8.47 (dd, *J* = 3.9, 1.0 Hz, 1H), 7.68 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.36 (m, 2H), 7.32-7.26 (m, 3H) overlaps with CDCl₃, 7.20 (dd, *J* = 4.9, 3.9 Hz, 1H), 6.48 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.44 (d, *J* = 5.8 Hz, 1H), 5.33 (dd, *J* = 4.4, 1.6 Hz, 1H), 4.62 (d, *J* = 15.0 Hz, 1H), 4.53 (d, *J* = 15.0 Hz, 1H), 4.21 (dd, *J* = 4.4, 4.0 Hz, 1H), 3.87 (d, *J* = 11.9 Hz, 1H), 3.59 (d, *J* = 11.9 Hz, 1H), 3.03 (d, *J* = 4.0 Hz, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 190.09, 172.90, 143.58, 136.55, 135.80, 134.54, 134.44, 133.40, 128.86, 128.75, 127.94, 127.76, 90.50, 81.38, 52.05 overlaps with 52.04, 48.84, 46.80. HRMS (ESI) calcd for C₂₀H₁₇NNaO₃S⁺ (MNa⁺) 374.0821, found 374.0821.



endo-6-Benzoyl-3-(2-thienylmethyl)-4-oxo-10-oxa-3-

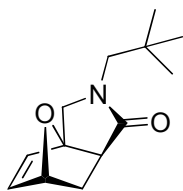
azatricyclo[5.2.1.0^{1,5}]dec-8-ene (3b): from 1.00 g of **1a** (5.68 mmol), 0.5 mL of DIC (3.23 mmol), 0.55 g of **2b** (2.85 mmol) and 1.0 mL of DIEA (5.74 mmol) (hexane/EtOAc gradient 20:1→10:1): 0.50 g (50%). ¹H NMR (500 MHz, CDCl₃) δ = 8.24 (d, *J* = 7.2 Hz,

2H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 2H), 7.26 (dd, $J = 5.0, 1.3$ Hz, 1H) overlaps with CDCl_3 , 7.01 (m, 1H), 6.97 (dd, $J = 5.0, 3.4$ Hz, 1H), 6.45 (d, $J = 5.8$ Hz, 1H), 6.35 (dd, $J = 5.8, 1.6$ Hz, 1H), 5.32 (dd, $J = 4.5, 1.6$ Hz, 1H), 4.83 (d, $J = 15.4$ Hz, 1H), 4.65 (d, $J = 15.4$ Hz, 1H), 4.33 (dd, $J = 4.5, 3.9$ Hz, 1H), 3.95 (d, $J = 11.8$ Hz, 1H), 3.67 (d, $J = 11.8$ Hz, 1H), 3.06 (d, $J = 3.9$ Hz, 1H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 196.92, 172.65, 138.27, 136.09$ overlaps with 136.08, 133.62, 133.59, 128.90, 128.80, 127.00, 126.82, 125.73, 90.55, 81.38, 51.50, 51.43, 48.68, 41.41. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{17}\text{NNaO}_3\text{S}^+$ (MNa^+) 374.0821, found 374.0822.



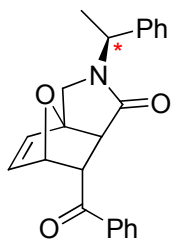
endo-**6-Benzoyl-3-neopentyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-**

8-ene (3c-1): from 1.00 g of **1a** (5.68 mmol), 0.54 g of EDC (2.82 mmol), 0.50 g of **2c** (2.99 mmol) and 1.0 mL of DIEA (5.74 mmol) (hexane/EtOAc gradient 20:1→10:1): 0.27 g (29%). ^1H NMR (500 MHz, CDCl_3) $\delta = 8.25$ (d, $J = 7.2$ Hz, 2H), 7.59 (t, $J = 7.3$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 2H), 6.49 (d, $J = 5.8$ Hz, 1H), 6.38 (dd, $J = 5.8, 1.6$ Hz, 1H), 5.32 (dd, $J = 4.5, 1.6$ Hz, 1H), 4.29 (dd, $J = 4.5, 3.8$ Hz, 1H), 4.16 (d, $J = 11.9$ Hz, 1H), 3.78 (d, $J = 11.9$ Hz, 1H), 3.37 (d, $J = 13.8$ Hz, 1H), 3.03 (d, $J = 3.8$ Hz, 1H), 2.97 (d, $J = 13.8$ Hz, 1H), 1.00 (s, 9H). ^{13}C NMR (500 MHz, CDCl_3) $\delta = 197.19, 173.91, 136.18, 136.12, 133.54$ (two overlapping peaks), 128.93, 128.76, 90.90, 81.40, 55.73, 52.71, 51.80, 51.10, 33.92, 28.34. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{23}\text{NNaO}_3^+$ (MNa^+) 348.1570, found 348.1554.



3-Neopentyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene (3c-2):

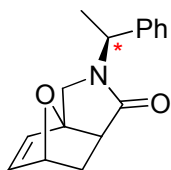
(*procedure B*) from 0.21 mL of acryloyl chloride (2.58 mmol) and 0.40 g of **2c** (2.39 mmol) at -78°C (hexane/EtOH gradient 20:1→10:1): 40 mg (8%). ¹H NMR (500 MHz, CDCl₃) δ = 6.43 (d, *J* = 5.8 Hz, 1H), 6.41 (dd, *J* = 5.8, 1.6 Hz, 1H), 5.07 (dd, *J* = 4.6, 1.6 Hz, 1H), 4.16 (d, *J* = 11.8 Hz, 1H), 3.78 (d, *J* = 11.8 Hz, 1H), 3.35 (d, *J* = 13.8 Hz, 1H), 2.93 (d, *J* = 13.8 Hz, 1H), 2.47 (dd, *J* = 8.8, 3.5 Hz, 1H), 2.20 (ddd, *J* = 11.8, 4.5, 3.6 Hz, 1H), 1.59 (dd, *J* = 11.8, 8.8 Hz, 1H), 0.99 (s, 9H). ¹³C NMR (500 MHz, CDCl₃) δ = 175.00, 137.09, 133.19, 89.29, 79.07, 55.57, 52.90, 47.15, 33.93, 28.32, 28.23.



***endo*-6-Benzoyl-3-[(1S)-1-phenylethyl]-4-oxo-10-oxa-3-**

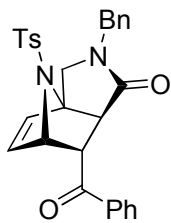
azatricyclo[5.2.1.0^{1,5}]dec-8-ene (inseparable mixture of two diastereomers) (**3d-1**): from 0.50 g of **1a** (2.84 mmol), 0.54 g of EDC (2.82 mmol), 0.57 g of **2d** (2.83 mmol) and 0.5 mL of DIEA (2.87 mmol) (hexane/EtOAc gradient 20:1→4:1): 0.40 g (40%). (*diastereomer a*) ¹H NMR (500 MHz, CDCl₃) δ = 8.26 (m, 2H), 7.60 (m, 1H), 7.51 (m, 2H), 7.40-7.30 (m, 4H), 7.26 (m, 1H) overlaps with CDCl₃, 6.46 (d, *J* = 5.8 Hz, 1H), 6.35 (dd, *J* = 5.7, 1.6 Hz, 1H), 5.58 (q, *J* = 7.1 Hz, 1H), 5.32 (d, *J* = 4.5 Hz, 1H), 4.35 (dd, *J* = 4.5, 3.8 Hz, 1H), 3.89 (d, *J* = 11.8 Hz, 1H), 3.45 (d, *J* = 11.8 Hz, 1H), 3.10 (d, *J* = 3.8 Hz, 1H), 1.60 (d, *J* = 7.2 Hz, 3H). (*diastereomer b*) ¹H NMR (500 MHz, CDCl₃) δ = 8.26

(m, 2H), 7.60 (m, 1H), 7.51 (m, 2H), 7.40-7.30 (m, 4H), 7.26 (m, 1H) overlaps with CDCl₃, 6.38 (d, *J* = 5.8 Hz, 1H), 6.34 (dd, *J* = 5.7, 1.6 Hz, 1H), 5.59 (q, *J* = 7.1 Hz, 1H), 5.32 (d, *J* = 4.5 Hz, 1H), 4.34 (dd, *J* = 4.5, 3.8 Hz, 1H), 3.61 (d, *J* = 11.9 Hz, 1H), 3.48 (d, *J* = 11.9 Hz, 1H), 3.04 (d, *J* = 3.8 Hz, 1H), 1.57 (d, *J* = 7.1 Hz, 3H). HRMS (ESI) calcd for C₂₃H₂₁NNaO₃⁺ (MNa⁺) 382.1414, found 382.1420.



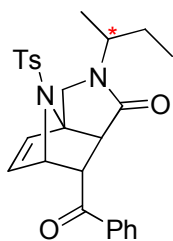
3-[(1S)-1-Phenylethyl]-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene

(separable mixture of two diastereomers) (**3d-2**): (*procedure B*) from 0.20 mL of acryloyl chloride (2.46 mmol) and 0.40 g of **2d** (1.99 mmol) at -78°C (hexane/EtOAc gradient 20:1→10:1): 76 mg (15%). (*diastereomer a*) ¹H NMR (500 MHz, CDCl₃) δ = 7.35-7.22 (m, 5H) overlaps with CDCl₃, 6.38 (m, 2H), 5.54 (q, *J* = 7.2 Hz, 1H), 5.06 (d, *J* = 4.5 Hz, 1H), 3.87 (d, *J* = 11.6 Hz, 1H), 3.43 (d, *J* = 11.6 Hz, 1H), 2.51 (dd, *J* = 8.8, 3.5 Hz, 1H), 2.24 (ddd, *J* = 11.8, 4.5, 3.6 Hz, 1H), 1.60 (dd, *J* = 11.8, 8.8 Hz, 1H) overlaps with 1.59 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (500 MHz, CDCl₃) δ = 173.70, 139.84, 137.14, 133.22, 128.55, 127.28, 126.69, 88.91, 79.01, 48.67, 47.95, 44.78, 28.10, 16.97.



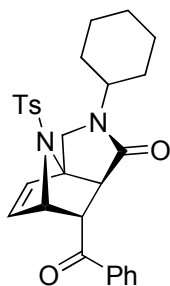
endo-6-Benzoyl-3-benzyl-10-(*p*-toluenesulfonyl)-4-oxo-3,10-

diazatricyclo[5.2.1.0^{1,5}]dec-8-ene (3g): (all the attempts to prepare the compound failed).



endo-6-Benzoyl-3-(1-methylpropyl)-10-(*p*-toluenesulfonyl)-4-oxo-3,10-

diazatricyclo[5.2.1.0^{1,5}]dec-8-ene (inseparable mixture of two diastereomers) (**3h**): from 0.71 g of **1a** (4.03 mmol), 0.40 g of EDC (2.09 mmol), 0.62 g of **2h** (2.02 mmol) and 0.7 mL of DIEA (4.02 mmol) (recrystallized from hexane/EtOAc/EtOH/DCM mixture): 0.43 g (46%). (*diastereomer a*) ¹H NMR (500 MHz, CDCl₃) δ = 8.24 (m, 2H), 7.59 (m, 1H), 7.55-7.48 (m, 4H), 7.27 (m, 2H), 5.94 (d, *J* = 5.7 Hz, 1H), 5.88 (dd, *J* = 5.7, 2.1 Hz, 1H), 5.10 (dd, *J* = 4.0, 2.0 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.33 (t, *J* = 4.1 Hz, 1H), 4.17 (m, 1H), 3.70 (d, *J* = 11.7 Hz, 1H), 2.96 (d, *J* = 4.2 Hz, 1H), 2.41 (s, 3H), 1.63 (m, 2H), 1.53 (m, 2H), 1.16 (d, *J* = 6.8 Hz, 1H), 0.90 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (500 MHz, CDCl₃) δ = 196.67, 171.39, 144.10, 136.56, 135.45, 133.97, 133.77, 131.94, 129.92, 129.07, 128.84, 127.99, 76.17, 67.39, 54.77, 48.94, 48.42, 41.66, 27.40, 21.59, 17.39, 11.17. (*diastereomer b*) ¹H NMR (500 MHz, CDCl₃) δ = 8.24 (m, 2H), 7.59 (m, 1H), 7.55-7.48 (m, 4H), 7.27 (m, 2H), 5.88 (d, *J* = 5.7 Hz, 1H), 5.85 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.08 (dd, *J* = 4.0, 2.0 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.33 (t, *J* = 4.1 Hz, 1H), 4.17 (m, 1H), 3.76 (d, *J* = 11.7 Hz, 1H), 2.91 (d, *J* = 4.3 Hz, 1H), 2.42 (s, 3H), 1.63 (m, 2H), 1.53 (m, 2H), 1.20 (d, *J* = 6.9 Hz, 1H), 0.97 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (500 MHz, CDCl₃) δ = 196.83, 171.32, 144.12, 136.44, 135.40, 134.05, 133.77 (overlaps with *diastereomer a*), 131.62, 129.94, 129.12, 128.80, 128.10, 75.97, 67.39 (overlaps with *diastereomer a*), 55.16, 49.23, 48.60, 42.03, 26.91, 21.59 (overlaps with *diastereomer a*), 18.00, 11.31. HRMS (ESI) calcd for C₂₆H₂₉N₂O₄S⁺ (MH⁺) 465.1843, found 465.1839.



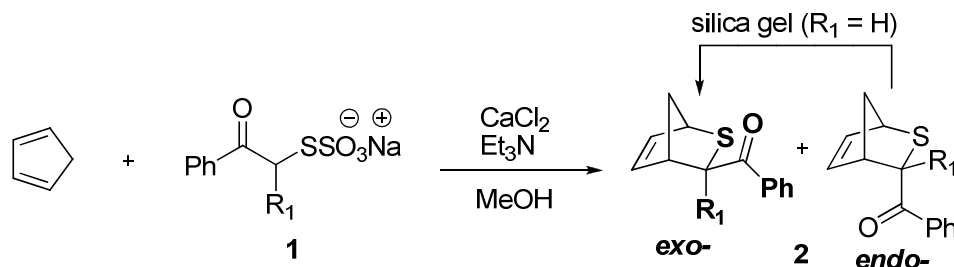
3-Cyclohexyl-endo-6-benzoyl-10-(*p*-toluenesulfonyl)-4-oxo-3,10-diazatricyclo[5.2.1.0^{1,5}]dec-8-ene (3i): from 0.71 g of **1a** (4.03 mmol), 0.40 g of EDC (2.09 mmol), 0.62 g of **2i** (1.86 mmol) and 0.7 mL of DIEA (4.02 mmol) (recrystallized from Hex/EtOAc/EtOH/DCM mixture): 0.34 g (37%). ¹H NMR (500 MHz, CDCl₃) δ = 8.26 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.27 (d, *J* = 7.4 Hz, 2H) overlaps with CDCl₃, 5.93 (m, 2H), 5.10 (dd, *J* = 3.8, 1.4 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.31 (t, *J* = 4.1 Hz, 1H), 3.98 (m, 1H), 3.76 (d, *J* = 11.7 Hz, 1H), 2.90 (d, *J* = 4.2 Hz, 1H), 2.42 (s, 3H), 1.83-1.75 (m, 3H), 1.68 (m, 2H), 1.47-1.32 (m, 4H), 1.13 (m, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 196.84, 170.95, 144.09, 136.60, 135.40, 134.27, 133.75, 131.83, 129.90, 129.10, 128.79, 127.99, 76.23, 67.27, 54.93, 51.16, 48.66, 42.65, 30.65, 29.64, 25.60, 25.39, 25.33, 21.58. HRMS (ESI) calcd for C₂₈H₃₀N₂NaO₄S⁺ (MNa⁺) 513.1818, found 513.1832.

D. Results and discussion – Part II.

Since furan- and pyrrol-based *H.-D.-A.* adducts did not produce the desired photochemical outcome, we decided to explore another approach to the *D.-A.* adducts containing one or multiple hetero-atoms in the bicyclic framework.

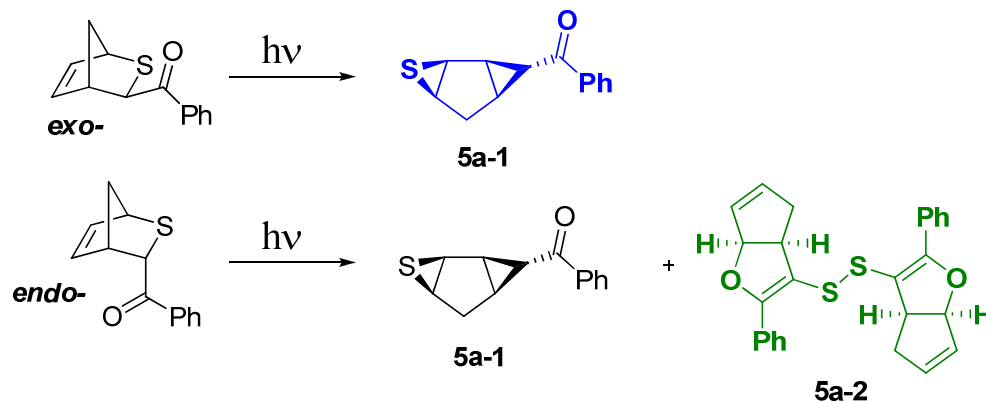
It is known that thioaldehydes and thioketones can react with various dienes yielding the *H.-D.-A.* adducts [44]. Given that thiocarbonyl compounds are unstable and tend to dimerize, they were generated in situ through the *Bunte* salts **1** (see Experimental

Section, page 133) and immediately reacted with freshly distilled cyclopentadiene (Scheme 39).



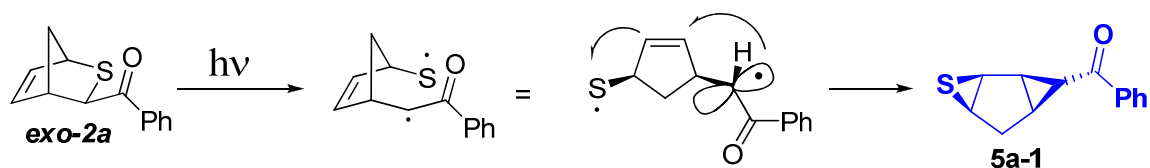
Scheme 39. Preparation of the *H*.-*D*.-*A*. adducts through the *Bunte* salts.

In most cases the formation of *exo*-adducts **2** was predominant. *Endo*-derivatives also are prone to rearrange into *exo*-products on a silica gel column. From our previous experience we learned that *exo*-adducts are usually photochemically inactive, therefore we were determined to focus only on the *endo*-adducts. But to our surprise *exo*-3-benzoyl-2-thiabicyclo[2.2.1]hept-5-enes **2** upon irradiation in a Rayonet photoreactor with RPR-3500 lamps or a UVLED-based illuminator with five 250 mW @ 365 nm Nichia chips rearranged giving thiirane **5a-1** as a major product (Scheme 40):



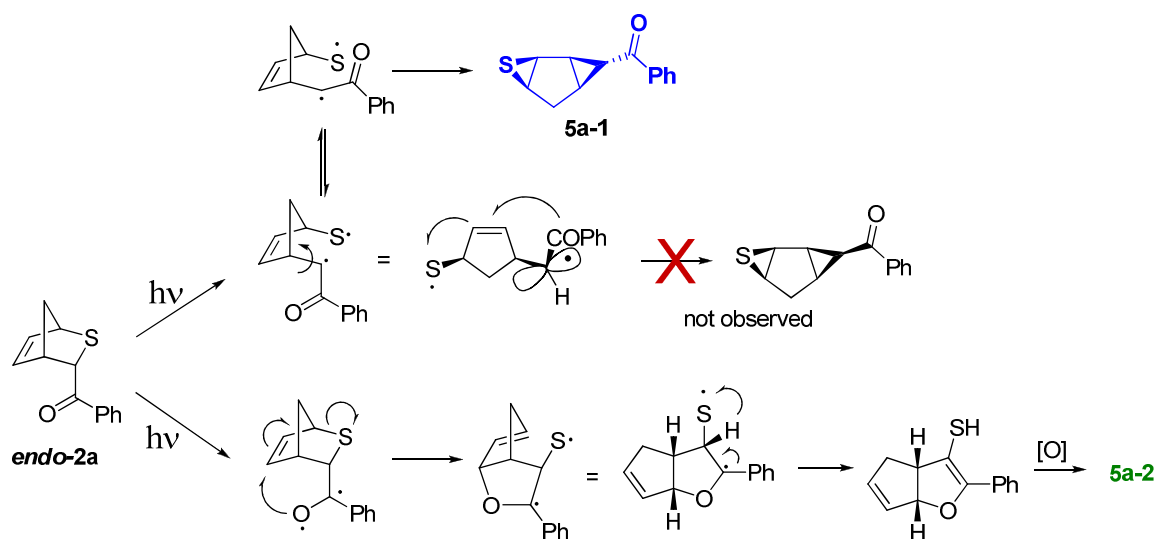
Scheme 40. Photolysis of *exo*- and *endo*-*H*.-*D*.-*A*. adducts **2**.

A plausible mechanism for the formation of **5a-1** involves a homolytic C-S bond fragmentation forming two radicals, which then react with the double bond, producing the final product. The thiirane and cyclopropyl rings are in a *syn*-configuration with respect to each other (Scheme 41):



Scheme 41. A plausible mechanism for the formation of thiirane **5a-1**.

Upon further investigation we discovered that *endo*-adduct **2a** did not undergo [2+2] cycloaddition forming an oxetane upon irradiation. Instead it produces 29% of disulfide **5a-2** along with thiirane **5a-1** discussed previously (Scheme 40).

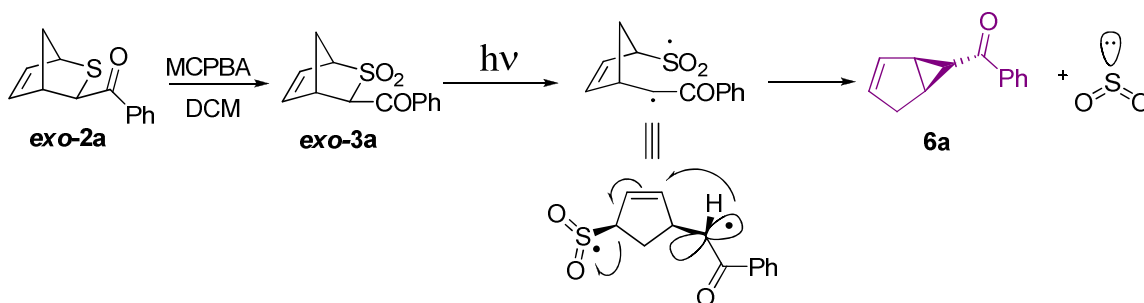


Scheme 42. A plausible mechanism for the formation of disulfide **5a-2**.

We suggest that *D.-A.* adduct **2** upon photolysis experiences homolytic C-S bond fragmentation along with C-O cleavage producing a 1,2-diradical. Only the *endo*-isomer produces product **5a-2**, because in this case the oxygen radical is properly positioned to

react with the double bond. The thiol, which is formed after H-migration, further oxidizes either on the column or during the photolysis yielding disulfide **5a-2** (Scheme 42), the structure of which was confirmed by X-ray crystallography (see Appendix D).

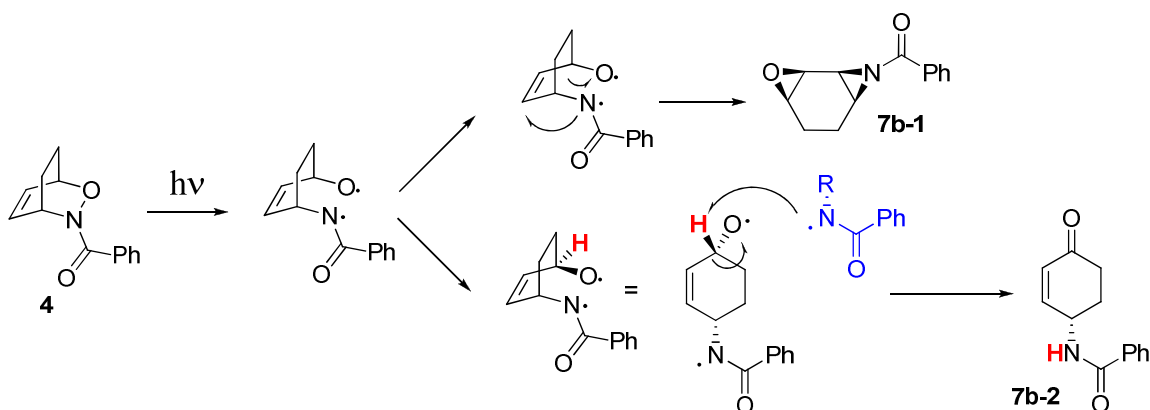
To better understand the mechanism and further explore the synthetic ability of this reaction we synthesized *exo*-*S,S*-dioxides **3** (see Experimental Section – Part II, page 136-137) [45] and irradiated them with an appropriate UV source (Scheme 43).



Scheme 43. Preparation of *S,S*-dioxide **exo-3a** and its photolysis.

We found that in these cases a double bond was formed instead of a thiirane ring due to the extrusion of sulfur dioxide upon photolysis of product **exo-3a**. A plausible mechanism for this transformation is shown in Scheme 43.

It should be mentioned that *D.-A.* adducts **4** containing 2-oxa-3-azabicyclo[2.2.*n*]alk-5-ene framework [45] undergo rearrangement upon irradiation similar to **exo-2a** (Scheme 44) producing compound **7b-1**. Although the irradiation of 3-benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene also resulted in the formation of amide **7b-2**, which was not observed in previous cases, this rearrangement most likely occurs via homolytic N-O bond fragmentation followed by an intramolecular H-abstraction yielding **7b-2** (Scheme 44).



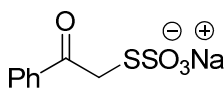
Scheme 44. A plausible mechanism for the formation of amide **7b-2**.

In conclusion, we discovered that although both *exo*- and *endo*-Sulfa-*D*.-*A*. adducts do not undergo [2+2] cycloaddition, they are, nonetheless, photochemically active. Various products with defined stereochemistry can be produced upon photolysis.

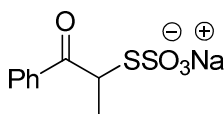
E. Experimental section – Part II.

1. Preparation of the *Bunte* salts (1):

Bromoacetophenone or 2-bromopropiophenone (1.0 eq) were dissolved in 10-50 mL of MeOH. Sodium thiosulfate (1.2 eq) was added to the solution followed by a few milliliters of water. The resulting mixture was then refluxed overnight. MeOH and water were removed on a high vacuum pump to give the *Bunte* salt, which was used without further purification.



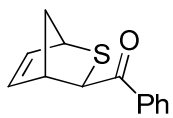
Sodium benzoymethanethiosulfonate (1a): from 2.0 g of bromoacetophenone (0.010 mol) and 1.9 g of Na₂S₂O₃ (0.012 mol). ¹H NMR (400 MHz, CD₃OD) δ = 8.05 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 4.61 (s, 2H).



Sodium 1-benzoyl-2-methyl-2-sulfonate (1b): from 4 mL of 2-bromopropiophenone (0.026 mol) and 5 g of Na₂S₂O₃ (0.032 mol). ¹H NMR (400 MHz, CD₃OD) δ = 8.16 (d, J = 7.3 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 5.14 (q, J = 6.8 Hz, 1H), 1.70 (d, J = 6.8 Hz, 3H).

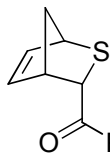
2. Preparation of the *Diels-Alder* adducts (2):

Triethylamine (10.0 eq) was added slowly with stirring to *Bunte* salt **1** (1.0 eq) in methanol containing cyclopentadiene (5.0 eq) and calcium chloride (1.0 eq) at room temperature. After 24 h, the mixture was acidified and extracted with DCM. The extract, after being freed from salts by washing successively with dilute hydrochloric acid, dilute sodium hydroxide, and water, contained the *endo*- and *exo*-adducts, which were separated by silica gel chromatography (eluted with hexane/EtOAc = 60:1→40:1) [44].

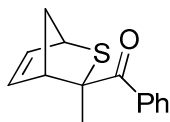


exo-3-Benzoyl-2-thiabicyclo[2.2.1]hept-5-ene (exo-2a): from 5.5 mL of Et₃N (39.46 mmol), 1.3 g of freshly distilled cyclopentadiene (19.67 mmol), 0.48 g of CaCl₂ (4.33 mmol) and 1.0 g of **1a** (3.93 mmol) (hexane/EtOAc gradient 60:1→40:1): before column purification - a mixture of *exo*- and *endo*-isomers by NMR, 58% and 42% respectively (mostly *exo*-adduct was recovered after the column). ¹H NMR (400 MHz, CDCl₃) δ = 7.95 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 6.47 (dd, J = 5.5, 2.8 Hz, 1H), 6.09 (dd, J = 5.5, 3.2 Hz, 1H), 4.16 (m, 1H), 4.06 (m, 1H), 3.67 (m, 1H), 1.89 (d, J = 9.5 Hz, 1H), 1.77 (ddd, J = 9.5, 2.2, 2.2 Hz, 1H). ¹³C NMR

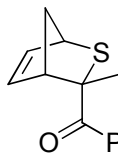
(400 MHz, CDCl₃) δ = 197.91, 138.79, 137.30, 133.48 overlaps with 133.47, 128.80, 128.45, 53.12, 52.43, 49.50, 46.71.



endo-3-Benzoyl-2-thiabicyclo[2.2.1]hept-5-ene (*endo-2a*): ¹H NMR (400 MHz, CDCl₃) δ = 7.94 (m, 2H), 7.55 (m, 1H), 7.45 (m, 2H), 6.38 (dd, J = 5.5, 2.9 Hz, 1H), 6.15 (dd, J = 5.5, 3.0 Hz, 1H), 5.12 (d, J = 3.5 Hz, 1H), 4.08 (m, 1H), 3.79 (m, 1H), 1.79 (m, 2H).



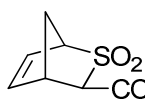
exo-3-Benzoyl-endo-3-methyl-2-thiabicyclo[2.2.1]hept-5-ene (*exo-2b*): from 5.5 mL of Et₃N (39.46 mmol), 1.3 g of freshly distilled cyclopentadiene (19.67 mmol), 0.48 g of CaCl₂ (4.33 mmol) and 1.0 g of **1b** (3.93 mmol) (hexane/EtOAc gradient 60:1→40:1): a mixture of *exo*- and *endo*-isomers by NMR, 66% and 34% respectively. ¹H NMR (500 MHz, CDCl₃) δ = 7.98 (m, 2H), 7.51 (m, 1H), 7.43 (m, 2H), 6.58 (d, J = 5.5, 2.8 Hz, 1H), 6.07 (d, J = 5.5, 3.3 Hz, 1H), 4.08 (m, 1H), 3.88 (m, 1H), 1.79 (ddd, J = 9.6, 2.3, 2.3 Hz, 1H), 1.74 (d, J = 9.6 Hz, 1H), 1.59 (s, 3H).



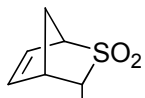
endo-3-Benzoyl-exo-3-methyl-2-thiabicyclo[2.2.1]hept-5-ene (*endo-2b*): All the attempts to obtain pure *endo-2b* failed. ¹H NMR (500 MHz, CDCl₃) δ = 7.90 (m, 2H), 7.50 (m, 1H), 7.40 (m, 2H), 6.26 (d, J = 5.4, 2.8 Hz, 1H), 6.20 (d, J = 5.4, 3.1 Hz, 1H), 4.07 (m, 1H), 3.52 (m, 1H), 2.02 (s, 3H), 1.98 (d, J = 9.5 Hz, 1H), 1.75 (ddd, J = 9.5, 2.3, 2.3 Hz, 1H).

3. Preparation of the [SO₂]-based adducts (3):

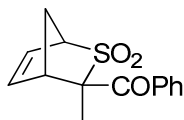
A solution of MCPBA (2.1 eq, 77% max) in DCM was added to a stirring solution of *exo*-adduct **2** (1.0 eq) in DCM at -78^oC, which was allowed to cool to room temperature overnight. The solution was washed with sat. solution of NaHCO₃, brine and extracted with DCM, then dried over Na₂SO₄, filtered, and concentrated in vacuo, affording pure product as a pale yellow solid [45].



exo-3-Benzoyl-2,2-dioxo-2-thiabicyclo[2.2.1]hept-5-ene (*exo*-**3a**): from 0.79 g of MCPBA (77%) (3.53 mmol) and 0.34 g of *exo*-**2a** (1.57 mmol): 0.38 g (97%). ¹H NMR (500 MHz, CDCl₃) δ = 8.05 (d, *J* = 7.4 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 6.67 (dd, *J* = 5.6, 2.8 Hz, 1H), 6.47 (dd, *J* = 5.6, 3.1 Hz, 1H), 4.22 (d, *J* = 2.5 Hz, 1H), 3.99 (m, 1H), 3.71 (m, 1H), 2.83 (d, *J* = 11.6 Hz, 1H), 2.47 (dddd, *J* = 11.6, 2.7, 2.7, 2.7 Hz, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 191.08, 141.99, 136.54, 134.30, 131.68, 129.06, 128.68, 66.27, 59.44, 44.39, 44.17.

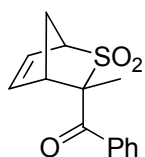


endo-3-Benzoyl-2,2-dioxo-2-thiabicyclo[2.2.1]hept-5-ene (*endo*-**3a**): All the attempts to obtain pure *endo*-**3a** failed.



exo-3-Benzoyl-endo-3-methyl-2,2-dioxo-2-thiabicyclo[2.2.1]hept-5-ene (*exo*-**3b**): from 0.82 g of MCPBA (77%) (3.66 mmol) and 0.40 g of *exo*-**2b** (1.74 mmol):

0.45 g (99%). ^1H NMR (500 MHz, CDCl_3) δ = 7.96 (m, 2H), 7.56 (m, 1H), 7.48 (m, 2H), 6.60 (dd, J = 5.7, 3.0 Hz, 1H), 6.41 (dd, J = 5.7, 3.2 Hz, 1H), 4.03 (m, 1H), 3.79 (m, 1H), 2.61 (d, J = 11.6 Hz, 1H), 2.41 (ddd, J = 11.6, 3.4, 2.3 Hz, 1H), 1.63 (s, 3H). ^{13}C NMR (500 MHz, CDCl_3) δ = 195.32, 140.77, 134.37, 133.21, 131.53, 130.07, 128.40, 67.53, 64.52, 49.88, 43.38, 23.22.

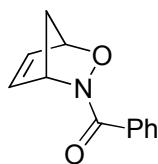


endo-3-Benzoyl-*exo*-3-methyl-2,2-dioxo-2-thiabicyclo[2.2.1]hept-5-ene

(*endo*-3b): All the attempts to obtain pure *endo*-3b failed.

4. Preparation of the [NO]-based adducts (4):

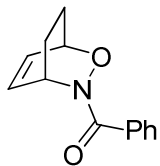
Benzhydroxamic acid (*N*-hydroxybenzamide) (1.0 eq) was dissolved in *i*-PrOH/ H_2O (acetone/ H_2O) mixture, cyclopentadiene (cyclohexadiene) was added dropwise (2.0-5.0 eq) followed by sodium periodate (1.1 eq). The resulting mixture was kept overnight at room temperature. After the reaction was completed, the mixture was washed with sat. solution of NaHCO_3 and extracted with DCM. Organic solvent was removed under vacuum [46].



3-Benzoyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (4a): from 0.5 g of

benzhydroxamic acid (3.65 mmol), 1.5 mL of cyclopentadiene (17.84 mmol) and 0.86 g of NaIO_4 (4.02 mmol). ^1H NMR (400 MHz, CDCl_3) δ = 7.76 (d, J = 7.4 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 6.51 (br. m, 1H), 6.38 (m, 1H), 5.34 (m, 1H)

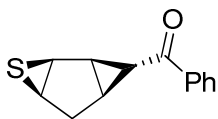
overlaps with 5.30 (br. m, 1H), 2.13 (ddd, $J = 8.7, 1.9, 1.9$ Hz, 1H), 1.85 (d, $J = 8.7$ Hz, 1H).



3-Benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (4b): from 0.5 g of benzhydroxamic acid (3.65 mmol), 1.0 mL of cyclopentadiene (10.50 mmol) and 0.86 g of NaIO₄ (4.02 mmol). ¹H NMR (400 MHz, CDCl₃) $\delta = 7.65$ (m, 2H), 7.44-7.36 (m, 3H), 6.65 (br. m, 1H) overlaps with 6.55 (m, 1H), 4.81 (br. m, 1H), 2.31 (br. m, 1H) overlaps with 2.24 (m, 2H), 1.62-1.48 (m, 2H).

5. Photolysis (5, 6, and 7):

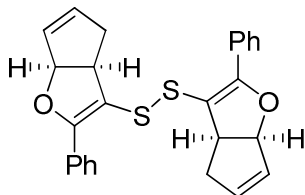
Approximately 0.01-0.1 M solution of a precursor **2** or **3** in benzene (or DCM) was irradiated in Pyrex vials in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) or a UVLED-based illuminator with five 250 mW @ 365 nm Nichia chips. The products were separated by silica gel chromatography (eluted with hexane/EtOAc = 40:1→30:1).



1R(S), 2S(R), 4R(S), 6R(S), 7R(S)-**7-Benzoyl-3-**

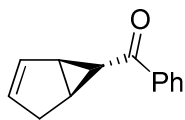
thiatribicyclo[4.1.0.0^{2,4}]heptane (5a-1): quantitative conversion from *exo*-**2a** and ~ 29% conversion from *endo*-**2a** by NMR. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.98$ (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 3.77 (dd, $J = 5.5, 4.2$ Hz, 1H), 3.58 (ddd, $J = 5.3, 2.2, 2.2$ Hz, 1H), 3.19 (dd, $J = 2.9, 2.9$ Hz, 1H), 2.52-2.44 (m, 2H), 2.41 (m, 1H), 2.12-2.07 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) $\delta = 197.41, 137.31, 132.96, 128.53, 128.20, 46.20, 44.05,$

37.49, 34.32, 31.48, 31.02. HRMS (ESI) calcd for $C_{13}H_{12}NaOS^+$ (MNa^+) 239.0501, found 239.0490.



1S(R), 5R(S)-**Di(3-phenyl-2-oxabicyclo[3.3.0]octa-3,7-diene-4-**

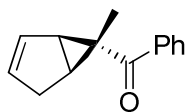
yl)disulfide (5a-2): ~ 29% conversion by NMR from *endo-2a* with 29% of **5a-1**, 16% of the unknown compound (possibly thiol) and 26% of the remaining *endo-2a*. 1H NMR (400 MHz, $CDCl_3$) δ = 7.77 (m, 2H), 7.40-7.36 (m, 3H), 5.95 (dddd, J = 5.7, 2.3, 2.3, 1.1 Hz, 1H), 5.62 (dddd, J = 5.7, 2.1, 2.1, 2.1 Hz, 1H), 4.54 (m, 1H), 3.07 (ddd, J = 9.1, 6.4, 3.4 Hz, 1H), 2.52 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 160.44, 135.70, 129.96, 129.26, 128.93, 128.19, 127.60, 104.54, 89.58, 46.28, 39.44. HRMS (ESI) calcd for $C_{13}H_{12}NaOS^+$ (MNa^+) 239.0501, found 239.0507.



1R(S), 5S(R), 6R(S)-**6-Benzylbicyclo[3.1.0]hex-2-ene (6a)**: All the

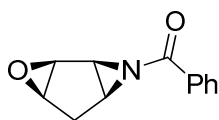
attempts to obtain pure **6a** failed, max 67% conversion (in 2 hours of irradiation by NMR). 1H NMR (500 MHz, $CDCl_3$) δ = 7.95 (m, 2H), 7.55 (m, 1H), 7.46 (m, 2H), 6.05 (dddd, J = 5.8, 2.0, 2.0, 2.0 Hz, 1H), 5.68 (m, 1H), 2.79 (dddd, J = 19.0, 6.4, 2.2, 2.2 Hz, 1H), 2.68 (dddd, J = 6.4, 2.2, 2.2, 2.2 Hz, 1H), 2.56 (dddd, J = 19.0, 2.3, 2.3, 2.3 Hz, 1H), 2.50 (ddd, J = 6.4, 6.4, 3.2 Hz, 1H), 2.02 (t, J = 2.7 Hz, 1H). 1H NMR (500 MHz, C_6D_6) δ = 7.89 (m, 2H), 7.13 (m, 1H), 7.06 (m, 2H), 5.76 (m, 1H), 5.35 (m, 1H), 2.71 (dddd, J = 6.3, 2.2, 2.2, 2.2 Hz, 1H), 2.48 (ddd, J = 6.4, 6.4, 3.0 Hz, 1H), 2.39 (dddd, J =

18.8, 6.5, 2.2, 2.2 Hz, 1H), 2.14 (dddd, $J = 18.8, 2.3, 2.3, 2.3$ Hz, 1H), 1.84 (t, $J = 2.7$ Hz, 1H).



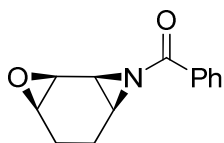
1R(S), 5S(R), 6R(S)-**6-Benzyl-6-methylbicyclo[3.1.0]hex-2-ene (6b)**: All

the attempts to obtain pure **6b** failed, max 64% conversion (in 30 min by NMR). The product is photochemically unstable and disappears in a 1.5 hours.



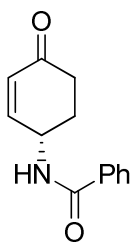
1S(R), 2S(R), 4R(S), 6S(R)-**7-Benzoyl-3-oxa-7-**

azatricyclo[4.1.0.0^{2,4}]heptane (7a): eluted with hexane/EtOH = 20:1→5:1 (< 25% by NMR after 48 h of irradiation). ¹H NMR (400 MHz, CDCl₃) δ = 7.99 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 3.79 (q, $J = 2.7$ Hz, 1H), 3.70 (dd, $J = 2.1, 2.1$ Hz, 1H), 3.50 (ddd, $J = 4.6, 4.6, 2.6$ Hz, 1H), 3.37 (dd, $J = 4.5, 1.7$ Hz, 1H), 2.42 (d, $J = 15.9$ Hz, 1H), 1.83 (ddd, $J = 15.9, 4.8, 3.0$ Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ = 176.84, 133.28, 132.51, 128.73, 128.41, 67.38, 53.36, 49.03, 40.99, 26.82.



1S(R), 2S(R), 4R(S), 7S(R)-**8-Benzoyl-3-oxa-8-**

azatricyclo[5.1.0.0^{2,4}]octane (7b-1): eluted with hexane/EtOH = 20:1→10:1 (< 36% by NMR after 48 h of irradiation). ¹H NMR (400 MHz, CDCl₃) δ = 8.06 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 3.49 (dd, $J = 4.2, 3.2$ Hz, 1H), 3.18 (ddd, $J = 4.2, 2.6, 2.6$ Hz, 1H), 2.98 (dd, $J = 6.2, 3.3$ Hz, 1H), 2.68 (m, 1H), 1.95-1.89 (m, 4H).



4-Benzoylamino-2-cyclohexen-1-one (7b-2): eluted with hexane/EtOH = 20:1→10:1 (~ 10% by NMR after 48 h of irradiation). ^1H NMR (400 MHz, CDCl_3) δ = 7.80 (d, J = 6.9 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 6.90 (ddd, J = 10.2, 2.6, 1.6 Hz, 1H), 6.35 (br. d, J = 7.8 Hz, NH), 6.08 (ddd, J = 10.2, 2.4, 0.8 Hz, 1H), 5.10 (dddd, J = 9.9, 8.3, 5.0, 2.5, 2.5 Hz, 1H), 2.61 (dddd, J = 16.9, 4.9, 4.9, 0.8 Hz, 1H) overlaps with 2.53 (ddd, J = 16.9, 12.2, 4.7 Hz, 1H), 2.44 (dddd, J = 12.7, 4.7, 4.7, 4.7, 1.6 Hz, 1H), 2.03 (dddd, J = 12.8, 12.2, 10.0, 4.9 Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ = 198.03, 167.08, 150.52, 133.76, 131.97, 130.54, 128.73, 126.98, 46.24, 36.24, 29.98.

Chapter Six: Direct screening of solution phase combinatorial libraries

A. Introduction.

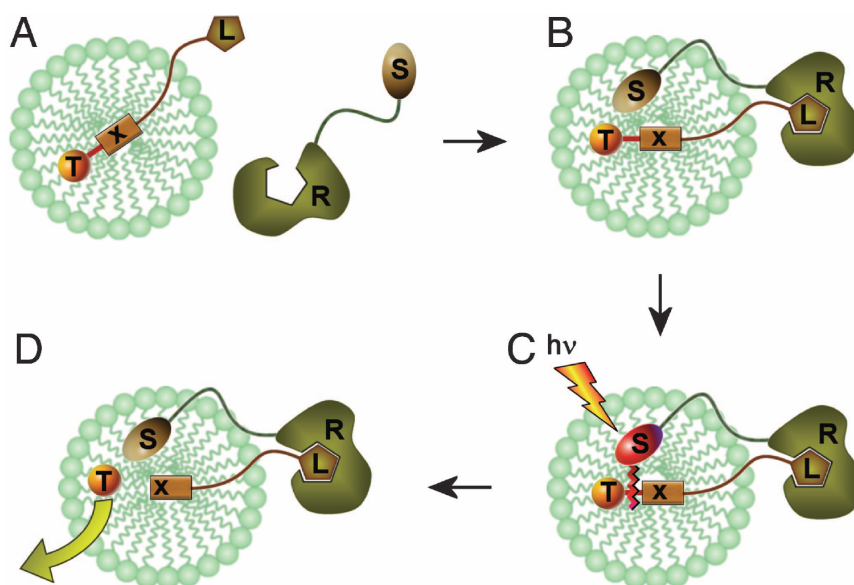
So far the synthetic application of photochemistry has been illustrated. In addition, “light” can be used also for screening of libraries.

High-throughput combinatorial chemistry is critical in modern drug discovery. Most massive high-throughput synthesis is achieved via the *split-and-mix* synthesis of libraries immobilized on polymeric support or beads [47]. Such one-bead/one-compound libraries are tested for the binding of biological targets through fluorescence-guided mechanical isolation of the beads. On the contrary, solution phase combinatorial chemistry holds even greater promise, as it is compatible with both divergent and convergent multistep synthesis, and not restricted to linear synthesis [48]. Its vast potential has not been fully recognized yet, due to the complexity of solution mixtures for binding. Although some deconvolution methods [49] have been developed to synthesize and screen soluble sub-libraries, all of them are time consuming, expensive and require multiple synthetic steps.

With collaboration of Dr. Rudresha Kottani, we have developed a technique for direct screening of solution phase libraries outfitted with photolabile tags [50].

B. Results and discussion.

The concept was based on 2-alkyl-1,3-dithiane adducts of carbonyl compounds, which were capable of efficient photo-assisted cleavage. This can happen only in the presence of an external electron transfer sensitizer (ETS) [Appendix E, 5-7, 9]. Central to this approach is the concept involving binary molecular systems in which the sensitizer and the 2-alkyl-1,3-dithiane-based photocleavable moiety are tethered to the particular components of a host - guest molecular recognition pair [51]. In such pairs, photoassisted fragmentation is dependent on a molecular recognition event, which makes the system photolabile. This model has been developed into a methodology for screening of either unsupported encoded libraries or encoded libraries immobilized on nanosized carriers. Scheme 45 gives a general sketch for screening the micelle-solubilized library of ligands L, encoded with tags T. The receptor R is outfitted with an ETS, which is shown in Scheme 45 as S.

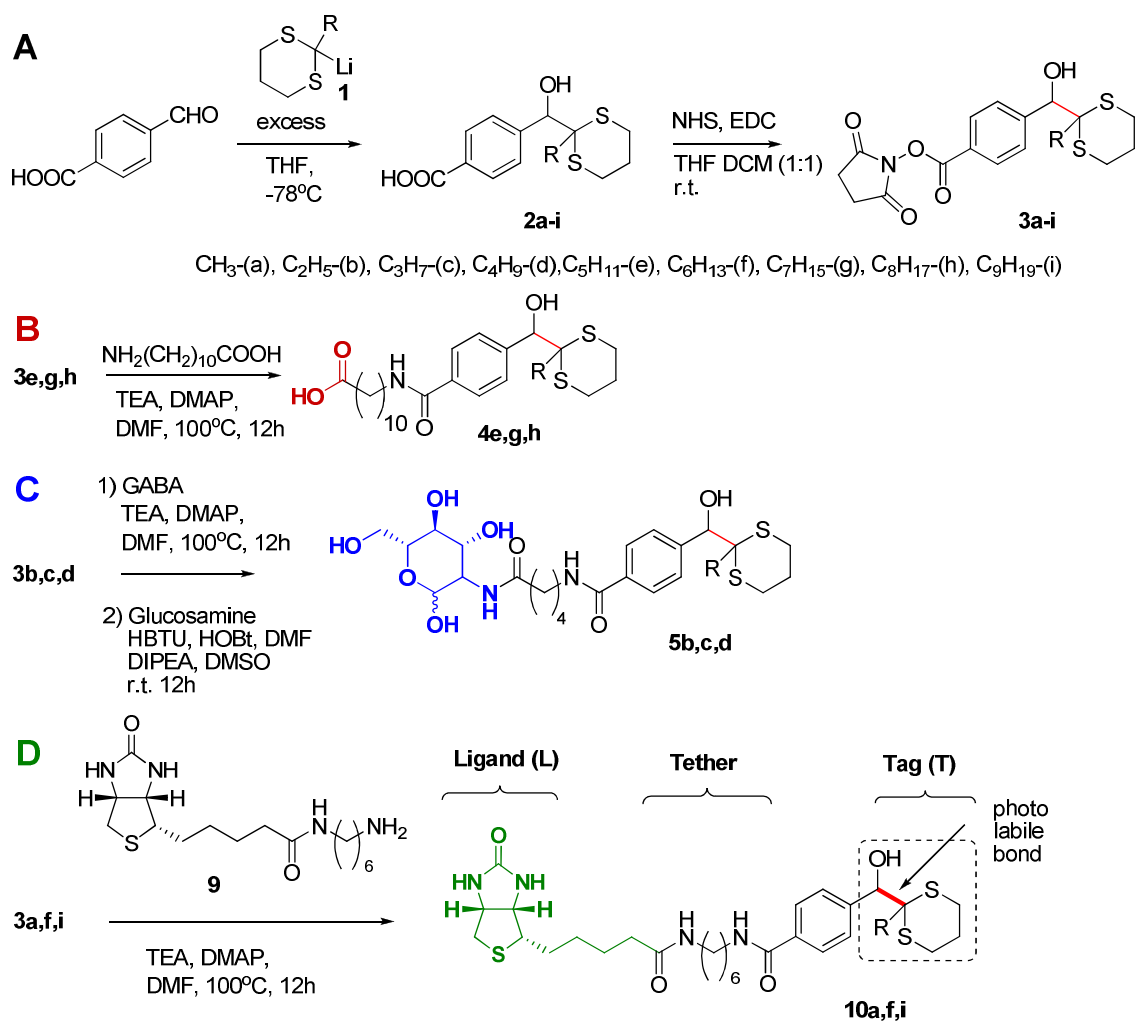


Scheme 45. The concept of a methodology for screening of encoded libraries.

Receptor R is incubated with the library of interest (A). The host - guest binding brings sensitizer S into the proximity of the adduct (B), which activates the release of dithiane tags upon irradiation (C-D). The main idea is to encode individual molecules. The n -th library member L_n can be encoded with a set of tags $\{T\}_m$, for example, T_1 , T_2 , and T_3 . One portion of L_n molecules is encoded with T_1 , another portion is encoded with T_2 , and the last one is encoded with T_3 . This leads to the fact that L_n is present in the solution as three subpopulations: L_n -tether- T_1 , L_n -tether- T_2 , and L_n -tether- T_3 . All of the tags encoding individual molecules of the bound ligand are released into the solution upon irradiation, revealing the nature of the compound of interest.

The tags should (a) be detectable at very low concentrations by standard analytical techniques; (b) not contain any functionality involved in biological interactions; (c) compatible with the synthetic steps; (d) be easy to separate from the aqueous environment; and (e) be available via a simple synthetic methodology. We found that 2-alkyl-1,3-dithianes meet those requirements and can be used for encoding in a binary fashion, where 1 indicates that free dithiane is present in the solution and 0 indicates that no dithiane is found.

We discovered that dithianes are especially appropriate for subpicomolar detection by GCMS. A better than 10:1 signal-to-noise ratio is achieved at a level of 500 femtomoles of alkyl dithianes per injection. The adducts of 2-alkyl-1,3-dithianes and 4-formylbenzoic acid were selected as a tagging unit because they add easily to aromatic aldehydes and the carboxylate acts as a handle to tie the tag to a ligand. A series of *N*-hydroxysuccinimide esters **3** were prepared as demonstrated in Scheme 46A [50].



Scheme 46. (A) Synthesis of *N*-hydroxysuccinimide esters **3**. (B-D) Synthesis of a model minilibrary containing three members [50].

To prove the theory, we selected a model host-guest system, based on biotin-avidin interaction, and synthesized a minilibrary of three members (Scheme 46B-D). Each compound was encoded with a set of three dithiane tags: carboxylates **4** were encoded with 2-pentyl, 2-heptyl and 2-octyl dithianes, sugars **6** (ethyl-, propyl-, and butyl), and biotins **10** (methyl-, hexyl-, and nonyl).

The receptor, avidin, was equipped with xanthone as an ETS [50]. The degree of immobilization was quantified by UV spectroscopy to be 0.77, indicating that each tetramer of avidin was carrying approximately three tethered molecules of xanthone carboxylates. A micellar detergent, dodecyl phosphocholine (DPC), was used preventing collisional quenching of avidin-tethered xanthone by unbound molecules.

Approximately 0.5 mg per tagged compound was solubilized in a 0.6 mL aqueous solution containing 60 mg of DPC. To this clear, micellar solution, 0.5 mL of avidin - xanthone conjugate was added, so the final concentrations were 0.7 mM of each library member carrying one tag, 23 μ M of protein, and 155 mM of DPC. The resulting micellar solution was incubated in an orbital shaker for 1 h, purged with argon for 45 min, and irradiated for 4 h by using a 335-nm filter. Then the mixture was extracted with 0.5 mL of hexane, concentrated to 100 μ L and analyzed by GCMS (Figure 17):

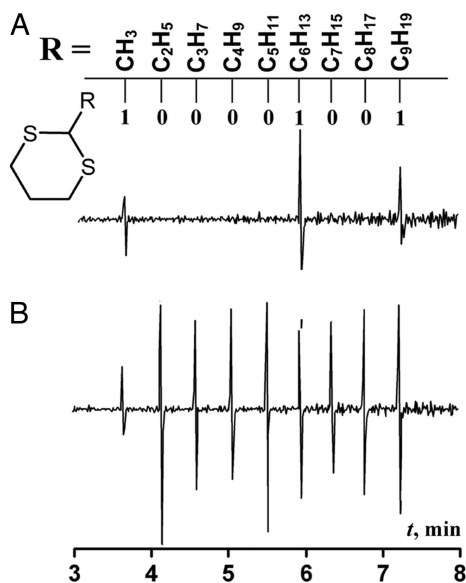


Figure 17. (A) The trace encoding biotin in binary 100100001 obtained after irradiation. (B) The trace for all nine alkyl dithianes at 1 pmol per injection [50].

It is clearly shown that only the biotin-encoding tags (methyl-, hexyl-, and nonyl-dithianes, binary 100100001, read from left to right), were identified in the chromatogram. The other six dithiane tags encoding glucosamine and aminoundecanoic acid were not apparent.

The quantum yield of alkyldithiane photo-release from ketone adducts increases in increments of 2 - 3% in a homologous series, leveling off for the higher alkyls [52].

The generality of this methodology is not restricted to the assemblies based on dithiane - aldehyde adducts. In general, any externally sensitized fragmentation reaction can be used in such binding assays. We obtained similar results with different tags containing thio-ortho-esters [53]. The model minilibrary was tagged with nine thio-ortho-esters, three tags per library member (see Figure 18). The DPC micellar solution of the library was incubated with the avidin-xanthone conjugate, irradiated and extracted with hexane. The GCMS trace again showed only the dithianes encoding biotin. None of the other six dithianes were detected in the hexane extract after irradiation.

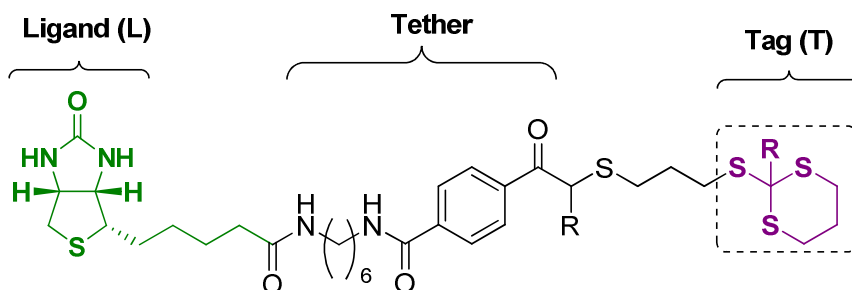


Figure 18. *Thio-ortho-esters*-encoded biotin [50].

In conclusion, we developed an approach to encoding and screening of solution phase libraries based on the photorelease of externally sensitized photolabile tags. The encoding tags can be released into solution only when a binding event occurs between the

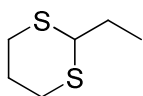
ligand and the receptor, equipped with an ETS. The released tags are analyzed in solution revealing the identity of the lead ligand or narrowing the range of potential leads.

C. Experimental section.

Common reagents were purchased from Sigma-Aldrich and used without further purification. THF was refluxed over and distilled from potassium benzophenone ketyl before use. ^1H and ^{13}C NMR spectra were recorded at 25°C on a Varian Mercury 400 MHz instrument, in CDCl_3 , DMSO-d_6 , or CD_3OD using TMS as an internal standard. Column chromatography was performed on silica gel, 70-230 mesh. The UV-visible spectra were recorded on a Beckman DU-640 spectrophotometer. Irradiations were carried out in a carousel Rayonet photo reactor equipped with RPR-3500 UV lamps (300- to 400-nm spectral distribution of irradiance density with a maximum at 350 nm) and a 335-nm long-pass solution filter. Gas chromatography was performed on a Varian Saturn 2100 T Ion-Trap instrument with electron ionization. Selective ion monitoring (m/z 119, 74) was used to detect dithiane tags after fragmentation (for more details see supporting information [50] and [53]).

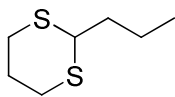
1. Preparation of 2-alkyl-1,3-dithianes (1):

To a solution of substituted aldehyde (66.9 mmol) and 1, 3-propanedithiol (66.9 mmol) in methylene chloride (300 mL) was added $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.268 mol) and the resulting solution was stirred for 12 h at 25°C. The reaction mixture was washed with NaOH (2 x 200 mL, 5% aq. soln) and H_2O (300 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum and dried to obtain the desired compound.



(1b): 91% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.01 (t, J = 6.79 Hz, 1H),

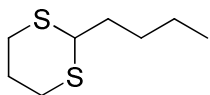
2.92-2.81 (m, 4H), 2.18-2.09 (m, 1H), 1.91-1.76 (m, 3H), 1.10 (t, J = 7.44 Hz, 3H).



(1c): 87% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.08 (t, J = 6.93 Hz,

1H), 2.92-2.79 (m, 4H), 2.15-2.08 (m, 1H), 1.91-1.80 (m, 1H), 1.75-1.70 (m, 2H), 1.57-

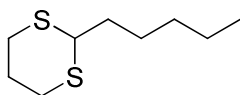
1.48 (m, 2H), 0.95 (t, J = 7.32 Hz, 3H);



(1d): 82% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.06 (t, J = 6.90 Hz,

1H), 2.92-2.79 (m, 4H), 2.15-2.08 (m, 1H), 1.91-1.81 (m, 1H), 1.78-1.72 (m, 2H), 1.52-

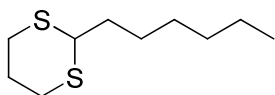
1.45 (m, 2H), 1.38-1.29 (m, 2H), 0.92 (t, J = 7.29 Hz, 3H).



(1e): 94% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.03 (t, J = 6.90

Hz, 1H), 2.92-2.79 (m, 4H), 2.15-2.08 (m, 1H), 1.92-1.80 (m, 1H), 1.77-1.71 (m, 2H),

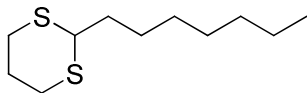
1.56-1.47 (m, 2H), 1.36-1.26 (m, 4H), 0.91 (t, J = 6.95 Hz, 3H).



(1f): 86% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.07 (t, J = 6.90

Hz, 1H), 2.92-2.79 (m, 4H), 2.15-2.08 (m, 1H), 1.92-1.83 (m, 1H), 1.77-1.72 (m, 2H),

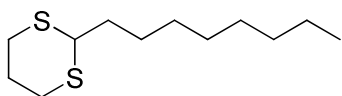
1.54-1.46 (m, 2H), 1.34-1.24 (m, 6H), 0.90 (t, J = 6.79 Hz, 3H).



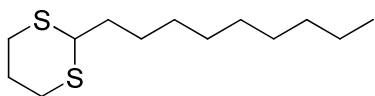
(1g): 91% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.06 (t, J =

6.90 Hz, 1H), 2.91-2.78 (m, 4H), 2.14-2.07 (m, 1H), 1.91-1.80 (m, 1H), 1.76-1.71 (m,

2H), 1.51-1.45 (m, 2H), 1.31-1.22 (m, 8H), 0.89 (t, J = 6.95 Hz, 3H).



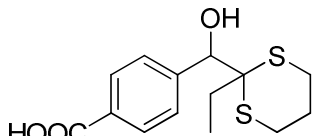
(**1h**): 93% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.05 (t, J = 6.89 Hz, 1H), 2.91-2.78 (m, 4H), 2.13-2.08 (m, 1H), 1.89-1.82 (m, 1H), 1.76-1.70 (m, 2H), 1.52-1.45 (m, 2H), 1.30-1.23 (m, 10H), 0.88 (t, J = 6.82 Hz, 3H).



(**1i**): 90% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.06 (t, J = 6.89 Hz, 1H), 2.91-2.78 (m, 4H), 2.15-2.08 (m, 1H), 1.91-1.80 (m, 1H), 1.76-1.70 (m, 2H), 1.52-1.47 (m, 2H), 1.32-1.22 (m, 12H), 0.89 (t, J = 6.88 Hz, 3H).

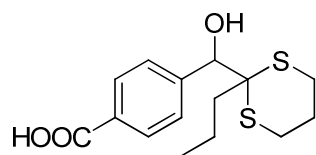
2. Preparation of the *Corey-Seebach* adducts (2):

n-BuLi (14.58 mL, 23.3 mmol, 1.6 M solution in THF) was added at -25°C to a solution of 2-alkyl-1,3-dithiane (23.3 mmol) in dry THF (40 mL) under nitrogen atmosphere. The resulting solution was stirred at this temperature for 2 h. The temperature was then reduced to -78°C and 4-formylbenzoic acid (0.5 g, 3.33 mmol) in 20 mL of THF was added. After stirring at -78°C for an additional 2 hr, the solution was allowed to warm to room temperature. Saturated ammonium chloride (20 mL) was added, and the aqueous phase was extracted twice with 20 mL ethyl acetate. The aqueous layer was acidified with 5% HCl, extracted with ethyl acetate (100 mL), dried over Na_2SO_4 and the solvent was removed under vacuum. The crude product was crystallized from toluene to get pure compound.

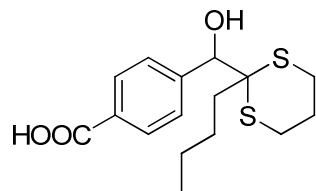


(**2b**): 96% Yield. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ = 7.85 (d, J = 8.34 Hz, 2H), 7.56 (d, J = 8.34 Hz, 2H), 5.68 (d, J = 4.50 Hz, 1H), 5.00 (d, J = 4.41

Hz, 1H), 3.06-2.99 (m, 1H), 2.91-2.84(m, 1H), 2.70-2.58 (m, 2H), 1.85-1.76 (m, 2H), 1.73-1.66 (m, 1H), 1.57-1.52 (m, 1H), 0.99 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (DMSO- d_6 , 100 MHz): $\delta = 168.00, 146.85, 130.24, 129.57, 128.49, 77.29, 58.95, 29.13, 26.46, 25.91, 24.86, 9.81$.



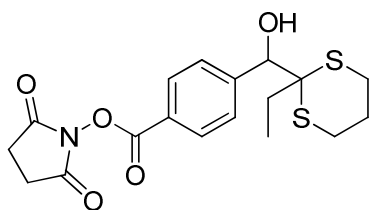
(**2c**): 94% Yield. ^1H NMR (DMSO- d_6 , 400 MHz): $\delta = 7.85$ (d, $J = 8.40$ Hz, 2H), 7.55 (d, $J = 8.28$ Hz, 2H), 5.68 (d, $J = 4.50$ Hz, 1H), 5.01 (d, $J = 4.50$ Hz, 1H), 3.06-3.03 (m, 1H), 2.90-2.87 (m, 1H), 2.68-2.59 (m, 2H), 1.84-1.83 (m, 1H), 1.72-1.66 (m, 2H), 1.51-1.40 (m, 3H), 0.82 (t, $J = 7.17$ Hz, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz): $\delta = 168.01, 146.82, 130.25, 129.54, 128.52, 77.32, 58.37, 38.63, 26.64, 26.09, 24.90, 18.16, 15.05$.



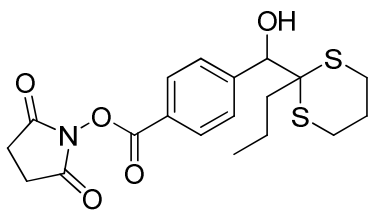
(**2d**): 92% Yield. ^1H NMR (DMSO- d_6 , 400 MHz): $\delta = 7.85$ (d, $J = 8.32$ Hz, 2H), 7.55 (d, $J = 8.28$ Hz, 2H), 5.68 (d, $J = 4.48$ Hz, 1H), 5.01 (d, $J = 4.44$ Hz, 1H), 3.08-3.03 (m, 1H), 2.92-2.87 (m, 1H), 2.68-2.58 (m, 2H), 1.86-1.66 (m, 3H), 1.49-1.40(m, 3H), 1.21-1.16 (m, 2H), 0.83 (t, $J = 7.31\text{Hz}$, 3H). ^{13}C NMR (DMSO- d_6 , 100 MHz): $\delta = 168.00, 146.86, 130.24, 129.55, 128.49, 77.33, 58.32, 36.11, 26.96, 26.62, 26.08, 24.90, 23.31, 14.64$.

3. Preparation of *N*-hydroxysuccinimide esters (3):

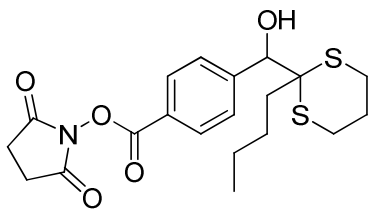
A mixture of 4-[(2-alkyl-1,3-dithian-2-yl)(hydroxyl)methyl]benzoic acid (1.60 mmol), *N*-hydroxysuccinimide (2.56 mmol) and EDC (2.08 mmol) was dissolved in THF:DCM (1:1.30 mL) and stirred for 24 h at room temperature. The solution was washed with 20 mL of water, 20 mL of saturated NaHCO₃, followed by 10 mL of brine. Then the solution was dried over anhydrous Na₂SO₄ and the solvent was evaporated under vacuum to give the desired compound.



(3b): 94% Yield. ¹H NMR (CDCl₃, 400 MHz): δ = 8.07 (d, *J* = 8.41 Hz, 2H), 7.67 (d, *J* = 8.41 Hz, 2H), 5.21 (s, 1H), 3.46 (br. s, 1H), 3.19-3.12 (m, 1H), 3.03-2.97 (m, 1H), 2.88-2.84 (m, 4H), 2.73-2.65 (m, 2H), 2.13-2.10 (m, 1H), 1.86-1.77 (m, 2H), 1.24-1.17 (m, 1H), 1.02 (t, *J* = 7.41 Hz, 3H). ¹H NMR (CD₃OD, 400 MHz): δ = 8.01 (d, *J* = 8.52 Hz, 2H), 7.72 (d, *J* = 8.39 Hz, 2H), 5.86 (d, *J* = 4.62 Hz, 1H), 5.07 (d, *J* = 4.63 Hz, 1H), 3.09-3.02 (m, 1H), 2.93-2.78 (m, 5H), 2.72-2.60 (m, 2H), 1.86-1.81 (m, 2H), 1.73-1.67 (m, 1H), 1.58-1.53 (m, 1H), 1.00 (t, *J* = 7.36 Hz, 3H). ¹³C NMR (CD₃OD, 100 MHz): δ = 171.04, 162.39, 149.95, 130.47, 129.19, 123.83, 76.88, 58.91, 29.05, 26.40, 26.23, 25.90, 24.81, 9.78.



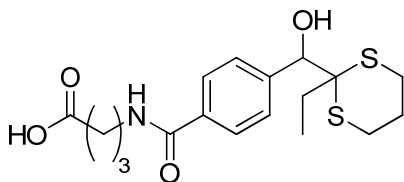
(3c): 97% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 8.07 (d, J = 8.04 Hz, 2H), 7.67 (d, J = 8.08 Hz, 2H), 5.20 (s, 1H), 3.49(br.s, 1H), 3.19-3.13 (m, 1H), 3.03-2.97 (m, 1H), 2.87-2.82 (m, 4H), 2.71-2.63 (m, 2H), 2.13-2.10 (m, 1H), 1.86-1.67 (m, 2H), 1.53-1.50 (m, 2H), 1.13-1.06 (m, 1H), 0.82 (t, J = 7.16 Hz, 3H). ^1H NMR (CD_3OD , 400 MHz): δ = 8.02 (d, J = 8.30 Hz, 2H), 7.72 (d, J = 8.36 Hz, 2H), 5.85 (d, J = 4.53 Hz, 1H), 5.09 (d, J = 4.52 Hz, 1H), 3.11-3.06 (m, 1H), 2.97-2.80 (m, 5H), 2.78-2.65 (m, 2H), 1.87-1.70 (m, 3H), 1.52-1.41 (m, 3H), 0.81 (t, J = 7.35 Hz, 3H); ^{13}C NMR (CD_3OD , 100 MHz): δ = 171.04, 162.39, 149.93, 130.44, 129.21, 123.83, 76.88, 58.32, 38.48, 26.57, 26.23, 26.12, 26.06, 24.84, 18.14, 15.03.



(3d): 93% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 8.06 (d, J = 8.20 Hz, 2H), 7.66 (d, J = 8.20 Hz, 2H), 5.19 (s, 1H), 3.49 (br. s, 1H), 3.19-3.12 (m, 1H), 3.02-2.96 (m, 1H), 2.86-2.81 (m, 4H), 2.71-2.62 (m, 2H), 2.13-2.09 (m, 1H), 1.85-1.70 (m, 2H), 1.52-1.47 (m, 2H), 1.22-1.08 (m, 3H), 0.84 (t, J = 7.16 Hz, 3H); ^1H NMR (CD_3OD , 400 MHz): δ = 8.03 (d, J = 8.23 Hz, 2H), 7.72 (d, J = 8.38 Hz, 2H), 5.85 (d, J = 4.57 Hz, 1H), 5.09 (d, J = 4.60 Hz, 1H), 3.11-3.05 (m, 1H), 2.95-2.78 (m, 5H), 2.68-2.60 (m, 2H), 1.88-1.67 (m, 3H), 1.50-1.41 (m, 3H), 1.23-1.17 (m, 2H), 0.84 (t, J = 7.30 Hz, 3H); ^{13}C NMR (CD_3OD , 100 MHz): δ = 171.04, 162.39, 149.95, 130.45, 129.19, 123.83, 76.91, 58.29, 36.00, 26.94, 26.58, 26.23, 26.06, 24.85, 23.28, 14.65.

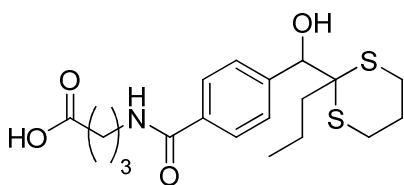
4. Preparation of sugar-based compounds (5 and 6):

To a mixture of 4-aminobutyric acid (1.70 mmol) and 1-({4-[2-alkyl-1,3-dithian-2-yl](hydroxyl)methyl]benzoyl}oxy)pyrrolidine-2,5-dione (1.13 mmol) in DMF (15 mL) was added triethylamine (2 mL) and a catalytic amount of DMAP. The resulting solution was stirred at 100°C for 12 h. This mixture was poured onto crushed ice and acidified with 5% HCl solution. This mixture was extracted with ethyl acetate (100 mL) and the organic layer was washed with water, dried over Na₂SO₄ and the solvent was evaporated to get the desired compound.



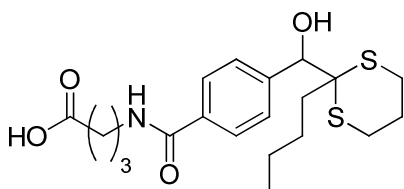
(5b): 91% Yield. ¹H NMR (CDCl₃, 400 MHz): δ = 7.70

(d, *J* = 8.44 Hz, 2H), 7.55 (d, *J* = 8.26 Hz, 2H), 6.80 (brt, *J* = 5.71 Hz, 1H), 5.17 (s, 1H), 3.51 (q, *J* = 12.60, 6.46 Hz, Hz, 2H), 3.18-3.11 (m, 1H), 3.03-2.96 (m, 1H), 2.73-2.64 (m, 2H), 2.46 (t, *J* = 6.85 Hz, 2H), 2.12-2.09 (m, 1H), 1.96-1.79 (m, 4H), 1.32-1.23 (m, 2H), 1.03 (t, *J* = 7.43 Hz, 3H). ¹H NMR (CD₃OD, 400 MHz): δ = 7.75 (d, *J* = 8.40 Hz, 2H), 7.62 (d, *J* = 8.27 Hz, 2H), 5.12 (s, 1H), 3.43 (t, *J* = 6.94 Hz, 2H), 3.06-3.02 (m, 1H), 2.90-2.85 (m, 1H), 2.69-2.60 (m, 2H), 2.40 (t, *J* = 7.35 Hz, 2H), 1.95-1.87 (m, 4H), 1.79-1.75 (m, 1H), 1.54-1.49 (m, 1H), 1.05 (t, *J* = 7.40 Hz, 3H). ¹³C NMR (CD₃OD, 100 MHz): δ = 175.88, 169.04, 143.98, 133.58, 129.03, 125.81, 76.08, 58.55, 39.29, 31.26, 28.70, 26.26, 25.45, 24.70, 24.42, 8.37.



(5c): 95% Yield. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.70$

(d, $J = 8.14$ Hz, 2H), 7.49 (d, $J = 8.16$ Hz, 2H), 7.15 (br. t, $J = 5.25$ Hz, 1H), 5.11 (s, 1H), 3.40 (q, $J = 12.04$, 5.95 Hz, 2H), 3.13-3.06 (m, 1H), 2.96-2.90 (m, 1H), 2.66-2.53 (m, 2H), 2.38 (t, $J = 6.79$ Hz, 2H), 2.10-1.97 (m, 1H), 1.86-1.67 (m, 4H), 1.54-1.39 (m, 2H), 1.22-1.13 (m, 2H), 0.85 (t, $J = 7.23$ Hz, 3H). ^1H NMR (CD_3OD , 400 MHz): $\delta = 7.75$ (d, $J = 8.39$ Hz, 2H), 7.62 (d, $J = 8.28$ Hz, 2H), 5.13 (s, 1H), 3.43 (t, $J = 6.94$ Hz, 2H), 3.12-3.05 (m, 1H), 2.95-2.89 (m, 1H), 2.67-2.59 (m, 2H), 2.40 (t, $J = 7.35$ Hz, 2H), 2.00-1.76 (m, 5H), 1.62-1.53 (m, 2H), 1.42-1.34 (m, 1H), 1.27 (t, $J = 7.31$ Hz, 3H). ^{13}C NMR (CD_3OD , 100 MHz): $\delta = 175.89$, 169.07, 143.97, 133.62, 129.01, 125.82, 76.08, 57.90, 39.28, 38.27, 31.26, 26.41, 25.60, 24.70, 24.45, 17.67, 13.70.

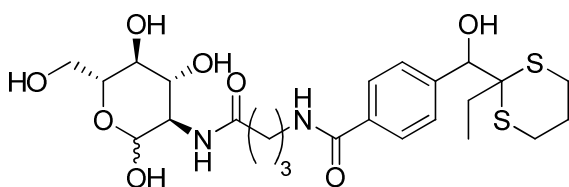


(5d): 97% Yield. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.76$

(d, $J = 8.20$ Hz, 2H), 7.55 (d, $J = 8.26$ Hz, 2H), 7.10 (br. t, $J = 5.42$ Hz, 1H), 5.12 (s, 1H), 3.42 (q, $J = 12.50$, 5.90 Hz, 2H), 3.13-3.04 (m, 1H), 2.97-2.91 (m, 1H), 2.67-2.56 (m, 2H), 2.39 (t, $J = 6.76$ Hz, 2H), 2.07-1.98 (m, 1H), 1.86-1.66 (m, 4H), 1.54-1.38 (m, 2H), 1.28-1.08 (m, 4H), 0.82 (t, $J = 7.21$ Hz, 3H). ^1H NMR (CD_3OD , 400 MHz): $\delta = 7.75$ (d, $J = 8.41$ Hz, 2H), 7.62 (d, $J = 8.35$ Hz, 2H), 5.14 (s, 1H), 3.43 (t, $J = 6.96$ Hz, 2H), 3.12-3.05 (m, 1H), 2.96-2.89 (m, 1H), 2.68-2.58 (m, 2H), 2.40 (t, $J = 7.36$ Hz, 2H), 1.98-1.75 (m, 5H), 1.61-1.48 (m, 2H), 1.45-1.37 (m, 1H), 1.27-1.18 (m, 2H), 0.88 (t, $J =$

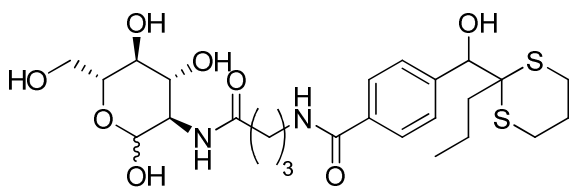
7.34Hz, 3H). ^{13}C NMR (CD_3OD , 100 MHz): δ = 175.87, 169.04, 143.96, 133.60, 129.02, 125.82, 76.05, 57.91, 39.29, 35.74, 31.26, 26.53, 26.44, 25.62, 24.70, 24.48, 23.10, 13.29.

To a mixture of **5a** (190 mg, 0.49 mmol), HBTU (206 mg, 0.54 mmol), and HOBt (73 mg, 0.54 mmol) in DMF (10 mL) was added DIPEA (0.2 mL, 1.08 mmol). The reaction mixture was then stirred for 5 min at ambient temperature. D-glucosamine hydrochloride (117 mg, 0.54 mmol) was dissolved in 1 mL DMSO, added to the above solution and stirred at room temperature for 12 h. The reaction mixture was poured into cold ether and allowed to settle down. The ether layer was decanted off and the brownish yellow material was washed with cold ether several times before drying. The product was purified by column chromatography using an eluent of 5% methanol in methylene chloride to give the desired compound.



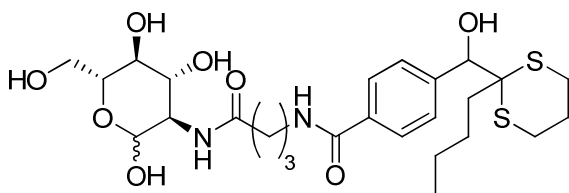
(**6b**): 65% Yield. ^1H NMR (CD_3OD , 400

MHz): δ = 7.77 (d, J = 8.46 Hz, 2H), 7.64 (d, J = 8.36 Hz, 2H), 5.12 (s, 1H), 5.10 (d, J = 3.45 Hz, α -anomer), 4.61 (d, J = 8.4 Hz, β -anomer), 3.89-3.65 (m, 5H), 3.47-3.32 (m, 3H), 3.11-3.04 (m, 1H), 2.94-2.87 (m, 1H), 2.71-2.61 (m, 2H), 2.36-2.32 (m, 2H), 2.00-1.87 (m, 4H), 1.83-1.74 (m, 1H), 1.58-1.49 (m, 1H), 1.39-1.27 (m, 1H), 1.06 (t, J = 7.41 Hz, 3H). ^{13}C NMR (CD_3OD , 100 MHz): δ = 174.85, 169.00, 144.09, 133.42, 129.03, 125.87, 91.42, 76.07, 71.92, 71.53, 71.26, 61.59, 58.53, 54.67, 39.18, 33.06, 28.68, 26.25, 25.56, 25.45, 24.42, 8.35.



(**6c**): 62% Yield. ^1H NMR (CD_3OD , 400

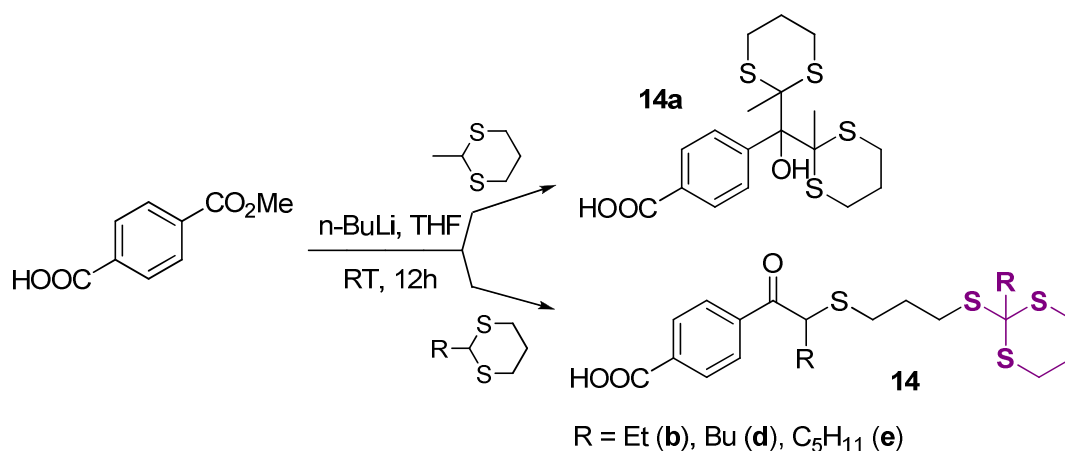
MHz): δ = 7.78 (d, J = 8.40 Hz, 2H), 7.63 (d, J = 8.32 Hz, 2H), 5.14 (s, 1H), 5.11 (d, J = 3.40 Hz, α -anomer), 4.62 (d, J = 8.36 Hz, β -anomer), 3.86-3.63 (m, 5H), 3.48-3.32 (m, 3H), 3.14-3.07 (m, 1H), 2.97-2.90 (m, 1H), 2.70-2.60 (m, 2H), 2.37-2.33 (m, 2H), 2.00-1.88 (m, 3H), 1.85-1.78 (m, 2H), 1.64-1.51 (m, 2H), 1.38-1.32 (m, 2H), 0.86 (t, J = 7.32 Hz, 3H). ^{13}C NMR (CD_3OD , 100 MHz): δ = 169.06, 144.08, 133.50, 128.98, 125.83, 125.81, 91.40, 76.12, 71.91, 71.50, 71.28, 61.60, 57.83, 54.68, 39.11, 38.30, 33.03, 28.69, 26.38, 25.57, 24.45, 17.62, 13.62.



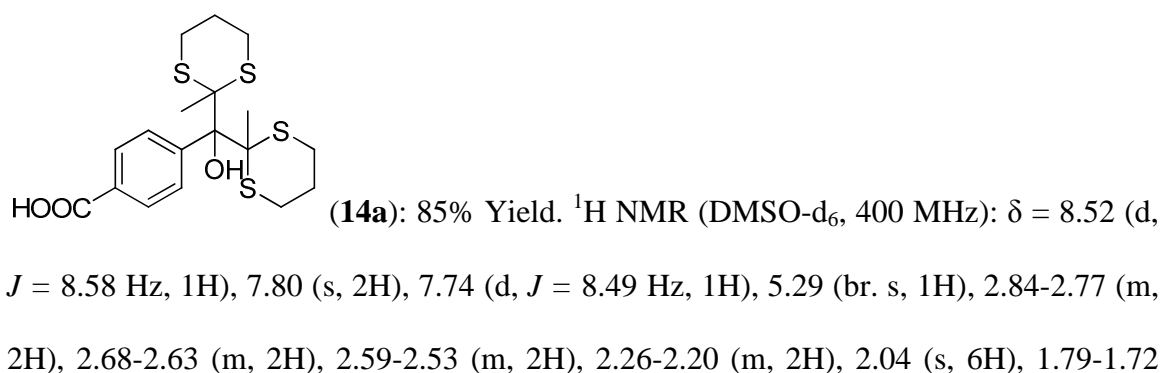
(**6d**): 56% Yield. ^1H NMR (CD_3OD , 400

MHz): δ = 7.77 (d, J = 8.45 Hz, 2H), 7.63 (d, J = 8.30 Hz, 2H), 5.14 (s, 1H), 5.11 (d, J = 3.41 Hz, α -anomer), 4.61 (d, J = 8.31 Hz, β -anomer), 3.84-3.61 (m, 5H), 3.45-3.35 (m, 3H), 3.14-3.05 (m, 1H), 2.97-2.90 (m, 1H), 2.69-2.58 (m, 2H), 2.36-2.32 (m, 2H), 2.00-1.88 (m, 5H), 1.59-1.48 (m, 2H), 1.38-1.34 (m, 2H), 1.29-1.18 (m, 2H), 0.89 (t, J = 7.33 Hz, 3H). ^{13}C NMR (CD_3OD , 100 MHz): δ = 174.74, 169.04, 144.04, 133.57, 128.98, 125.79, 91.40, 76.13, 71.92, 71.46, 71.31, 61.63, 57.83, 54.71, 51.51, 39.12, 35.78, 33.13, 26.49, 26.39, 25.59, 24.46, 23.06, 17.58, 13.18.

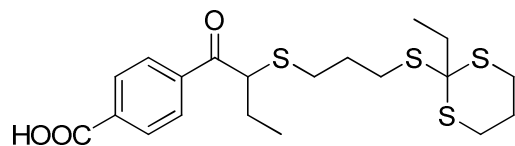
5. Preparation of thio-ortho-esters (14):



n-BuLi (8.96 mL, 14.3 mmol, 1.6 M solution in THF) was added at 20°C to a mixture of 2-alkyl-1,3-dithiane (14-17 mmol) in 50 mL of dry THF. The resulting solution was stirred at this temperature for 15 min. Monomethylterephthalate (516 mg, 2.86 mmol) in THF (30 mL) was added to the generated dithiane anion and the solution was stirred overnight. Aqueous work-up included quenching with saturated NH₄Cl (20 mL) followed by extraction with ethyl acetate (3x50 mL). The organic layer was dried over Na₂SO₄ and the solvent was removed under vacuum. The crude product was purified by chromatography on a slurry-packed silica gel column using 10% EtOAc-hexane as eluent.

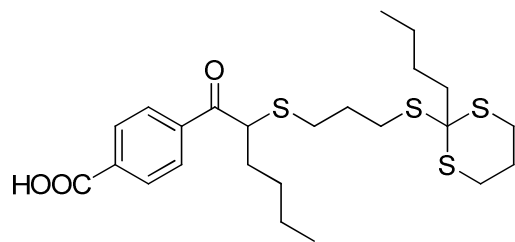


(m, 2H), 1.59-1.49 (m, 2H). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ = 168.10, 146.65, 131.26, 130.62, 129.92, 127.47, 126.46, 86.95, 63.29, 28.85, 27.97, 26.48, 24.51.



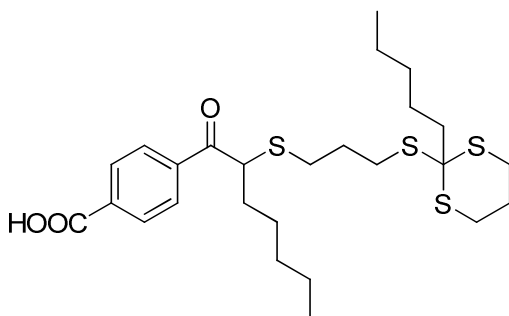
(**14b**): 82% Yield. ^1H NMR (CDCl_3 , 400 MHz):

δ = 8.21 (d, J = 8.58 Hz, 2H), 8.62 (d, J = 8.62 Hz, 2H), 4.05 (t, J = 7.30 Hz, 1H), 3.28-3.20 (m, 2H), 2.63-2.57 (m, 3H), 2.51-2.44 (m, 3H), 2.13-2.05 (m, 2H), 1.99-1.90 (m, 3H), 1.82-1.73 (m, 3H), 1.11 (t, J = 7.38 Hz, 3H), 1.06 (t, J = 7.33 Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 194.85, 170.59, 140.58, 132.97, 130.66, 128.74, 63.58, 49.35, 36.07, 31.87, 28.89, 28.19, 27.53, 25.29, 23.34, 14.60, 12.24, 9.07.



(**14d**): 86% Yield. ^1H NMR (CDCl_3 , 400 MHz):

δ = 8.20 (d, J = 8.68 Hz, 2H), 8.08 (d, J = 8.75 Hz, 2H), 4.12 (t, J = 7.38 Hz, 1H), 3.29-3.21 (m, 2H), 2.64-2.42 (m, 6H), 2.12-2.04 (m, 2H), 1.94-1.90 (m, 2H), 1.85-1.75 (m, 4H), 1.63-1.55 (m, 2H), 1.40-1.29 (m, 6H), 0.93-0.89 (m, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 194.83, 171.45, 140.48, 133.17, 130.63, 128.72, 62.82, 47.47, 42.91, 31.97, 29.86, 29.82, 28.87, 28.25, 27.58, 26.47, 25.29, 22.92, 22.76, 14.21, 14.20, 14.15.

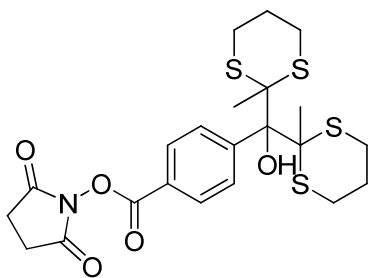


(**14e**): 85% Yield. ^1H NMR (CDCl_3 , 400 MHz):

δ = 8.21 (d, J = 8.67 Hz, 2H), 8.08 (d, J = 8.70 Hz, 2H), 4.12 (t, J = 7.33 Hz, 1H), 3.29-3.20 (m, 2H), 2.60-2.42 (m, 6H), 2.10-2.04 (m, 2H), 1.93-1.75 (m, 6H), 1.64-1.57 (m, 2H), 1.38-1.21 (m, 10H), 0.90 (t, J = 7.07 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 194.83, 171.57, 140.57, 133.00, 130.66, 128.73, 62.87, 47.52, 43.15, 31.98, 31.95, 31.81, 30.11, 28.90, 28.27, 27.60, 27.59, 27.35, 25.29, 24.02, 22.72, 22.69, 14.26, 14.25.

6. Preparation of *N*-hydroxysuccinimide thio-ortho-esters (**15**):

A mixture of **14a** (900 mg, 2.16 mmol), *N*-hydroxysuccinimide (398 mg, 3.46 mmol) and EDC (539 mg, 2.81 mmol) was dissolved in DMF (30 mL) and stirred for 24 h at room temperature. The solution was poured onto crushed ice and the solid was obtained by vacuum filtration, washed with water and dried to give pure **15a**.

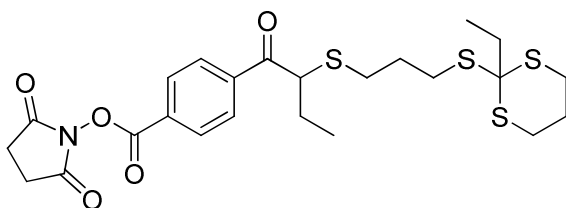


(**15a**): 96% Yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 8.36

(dd, J = 8.53, 1.90 Hz, 1H), 8.12 (dq, J = 8.44, 1.94 Hz, 2H), 8.04 (dd, J = 8.52, 1.94 Hz, 1H), 4.50 (s, 1H), 2.90-2.80 (m, 8H), 2.75-2.70 (m, 4H), 2.16 (s, 6H), 1.96-1.78 (m, 4H).

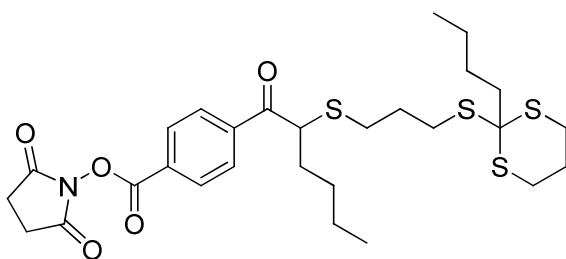
^{13}C NMR (CDCl_3 , 100 MHz): δ = 169.53, 161.92, 147.43, 130.52, 130.08, 129.46, 127.94, 124.45, 86.41, 63.41, 28.75, 27.94, 27.77, 25.92, 24.02.

A mixture **14b** (2.95 mmol), *N*-hydroxysuccinimide (4.72 mmol) and EDC (3.83 mmol) was dissolved in CH_2Cl_2 (30 mL) and stirred for 24 h at room temperature. The solution was washed with 20 mL water, 20 mL of saturated NaHCO_3 , followed by 10 mL of brine. Then the solution was dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuum to give the desired compound.



(**15b**): 92% Yield. ^1H NMR (CDCl_3 , 400

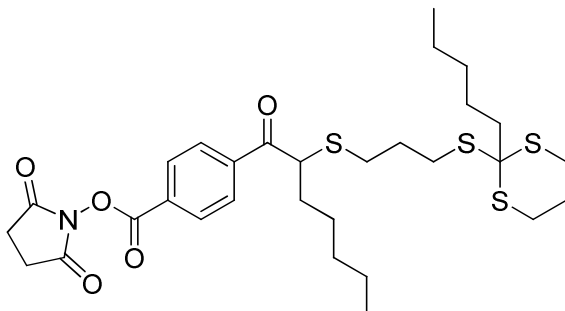
MHz): δ = 8.23 (d, J = 8.74 Hz, 2H), 8.11 (d, J = 8.44 Hz, 2H), 4.02 (t, J = 7.36 Hz, 1H), 3.27-3.19 (m, 2H), 2.92 (br. s, 4H), 2.62-2.38 (m, 6H), 2.12-2.05 (m, 2H), 2.00-1.74 (m, 6H), 1.12 (t, J = 7.38 Hz, 3H), 1.06 (t, J = 7.33 Hz, 3H).



(**15d**): 93% Yield. ^1H NMR (CDCl_3 , 400

MHz): δ = 8.22 (d, J = 8.74 Hz, 2H), 8.10 (d, J = 8.77 Hz, 2H), 4.09 (t, J = 7.35 Hz, 1H), 3.28-3.19 (m, 2H), 2.92 (br. s, 4H), 2.61-2.44 (m, 6H), 2.10-2.02 (m, 2H), 1.95-1.87 (m, 2H), 1.85-1.72 (m, 4H), 1.62-1.54 (m, 2H), 1.38-1.24 (m, 6H), 0.92-0.88 (m, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 194.36, 169.25, 161.35, 141.34, 130.98, 128.95, 128.74,

62.88, 47.61, 42.93, 31.97, 29.77, 29.74, 28.87, 28.23, 27.60, 26.47, 25.91, 25.27, 22.91, 22.73, 14.19.

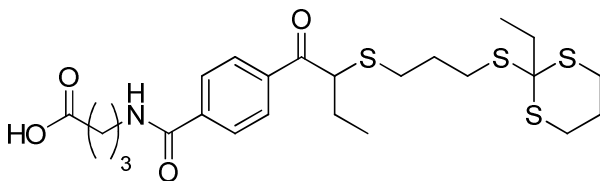


(**15e**): 97% Yield. ^1H NMR (CDCl_3 , 400

MHz): δ = 8.23 (d, J = 8.33 Hz, 2H), 8.10 (d, J = 8.36 Hz, 2H), 4.09 (t, J = 7.37 Hz, 1H), 3.28-3.20 (m, 2H), 2.92 (br. s, 4H), 2.60-2.45 (m, 6H), 2.11-2.01 (m, 2H), 1.94-1.90 (m, 2H), 1.86-1.73 (m, 4H), 1.65-1.56 (m, 2H), 1.38-1.22 (m, 10H), 0.90 (t, J = 7.05 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 194.39, 169.30, 161.36, 141.36, 130.97, 128.95, 128.73, 62.87, 47.65, 43.14, 31.97, 31.92, 31.77, 29.98, 28.90, 28.24, 27.58, 27.28, 25.91, 25.26, 24.01, 22.69, 22.66, 14.25, 14.23.

7. Preparation of sugar-based thio-ortho-esters (**17** and **18**):

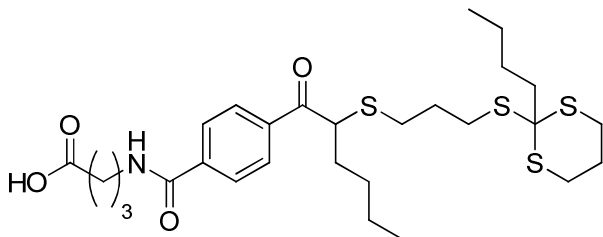
To a mixture of 4-aminobutyric acid (0.63 mmol) and **15b** (0.57 mmol) in DMF (15 mL) was added triethylamine (2 mL) and a catalytic amount of DMAP. The resulting solution was stirred at 100°C for 12 h, poured onto crushed ice and acidified with 5% HCl solution. The solid obtained was filtered, washed with water and dried to give pure **17b**.



(**17b**): 92% Yield. ^1H NMR (CDCl_3 , 400

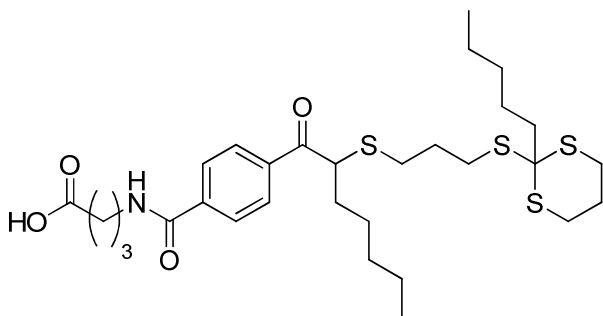
MHz): δ = 8.03 (d, J = 8.31 Hz, 2H), 7.87 (d, J = 8.29 Hz, 2H), 6.85 (br. t, J = 5.55 Hz,

1H), 4.04 (t, $J = 7.34$ Hz, 1H), 3.57 (q, $J = 12.40$, 6.35 Hz, 2H), 3.27-3.19 (m, 2H), 2.61-2.40 (m, 8H), 2.09-1.71 (m, 10H), 1.10 (t, $J = 7.38$ Hz, 3H), 1.04 (t, $J = 7.32$ Hz, 3H).



(**17d**): 87% Yield. ^1H NMR (CDCl_3 , 400

MHz): $\delta = 8.04$ (d, $J = 8.38$ Hz, 2H), 7.87 (d, $J = 8.40$ Hz, 2H), 6.75 (br. t, $J = 5.54$ Hz, 1H), 4.11 (t, $J = 7.40$ Hz, 1H), 3.58 (q, $J = 12.42$, 6.10 Hz, 2H), 3.30-3.21 (m, 2H), 2.60-2.47 (m, 8H), 2.01-1.90 (m, 10H), 1.62-1.54 (m, 2H), 1.38-1.31 (m, 6H), 0.92 (t, $J = 7.28$ Hz, 6H).

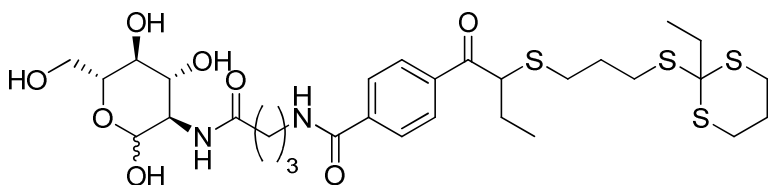


(**17e**): 90% Yield. ^1H NMR (CDCl_3 , 400

MHz): $\delta = 8.04$ (d, $J = 8.51$ Hz, 2H), 7.87 (d, $J = 8.52$ Hz, 2H), 6.72 (br. t, $J = 5.55$ Hz, 1H), 4.11 (t, $J = 7.32$ Hz, 1H), 3.58 (q, $J = 12.38$, 6.05 Hz, Hz, 2H), 3.28-3.20 (m, 2H), 2.61-2.43 (m, 8H), 2.10-1.84 (m, 10H), 1.64-1.58 (m, 2H), 1.50-1.45 (m, 1H), 1.34-1.25 (m, 9H), 0.90 (t, $J = 7.07$ Hz, 6H).

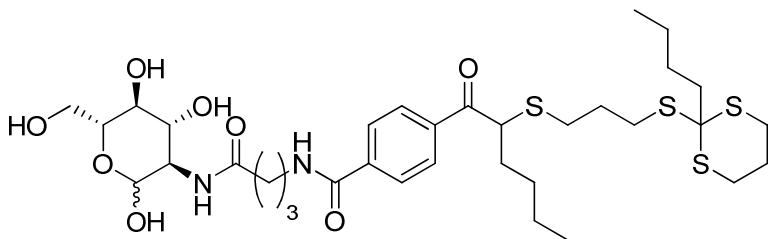
To a mixture of **17b** (0.26 mmol), HBTU (0.29 mmol), and HOBT (0.29 mmol) in DMF (10 mL) was added DIPEA (0.58 mmol) and the reaction mixture was stirred for 5 min at ambient temperature. D-glucosamine hydrochloride (0.29 mmol) was dissolved in 1 mL of DMSO and added to the above reaction mixture and stirred at room temperature

for 12 h. The solution was poured into cold ether and allowed to settle. The ether layer was decanted off and the brownish-yellow material was washed with cold ether several times and poured onto crushed ice, the obtained solid was filtered and washed with water, hexane to get the pure **18b**.



(18b): 65% Yield. ^1H NMR

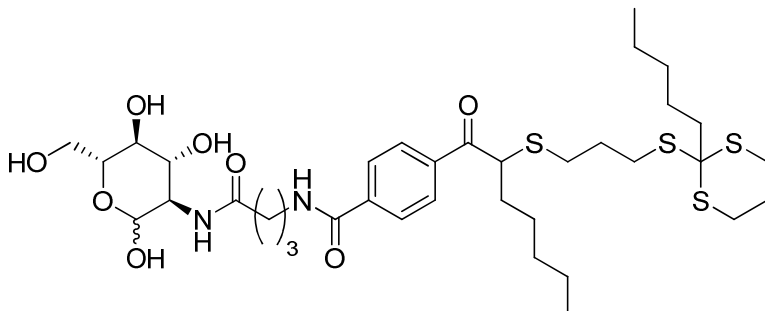
(CD_3OD , 400 MHz): δ = 8.11 (d, J = 8.69 Hz, 2H), 7.94 (d, J = 8.67 Hz, 2H), 5.11 (d, J = 3.47 Hz, α -anomer), 4.61 (d, J = 8.32 Hz, β -anomer), 4.30 (t, J = 7.32 Hz, 1H), 3.88-3.61 (m, 4H), 3.48-3.34 (m, 4H), 3.23-3.14 (m, 2H), 2.61-2.54 (m, 3H), 2.49-2.43 (m, 3H), 2.37-2.32 (m, 2H), 2.09-2.01 (m, 2H), 1.96-1.81 (m, 6H), 1.78-1.65 (m, 3H), 1.06 (m, 6H). ^{13}C NMR (CD_3OD , 100 MHz): δ = 195.79, 174.68, 167.95, 138.81, 138.34, 128.60, 127.47, 91.41, 71.94, 71.47, 71.30, 63.15, 61.64, 54.70, 48.79, 39.32, 35.73, 33.18, 31.33, 28.73, 28.01, 27.11, 27.10, 25.51, 25.08, 23.24, 11.02, 8.08.



(18d): 64% Yield. ^1H NMR

(CD_3OD , 400 MHz): δ = 8.10 (d, J = 8.44 Hz, 2H), 7.94 (d, J = 8.30 Hz, 2H), 5.11 (d, J = 3.58 Hz, α -anomer), 4.61 (d, J = 8.34 Hz, β -anomer), 4.35 (t, J = 7.32 Hz, 1H), 3.89-3.68 (m, 4H), 3.48-3.34 (m, 4H), 3.24-3.15 (m, 2H), 2.64-2.44 (m, 6H), 2.37-2.31 (m, 2H), 2.07-1.77 (m, 11H), 1.60-1.47 (m, 3H), 1.41-1.26 (m, 5H), 0.94-0.88 (m, 6H). ^{13}C NMR (CD_3OD , 100 MHz): δ = 195.70, 174.66, 167.94, 138.80, 138.36, 128.58, 127.47,

91.40, 71.93, 71.46, 71.31, 62.36, 61.63, 54.70, 46.99, 42.66, 39.30, 33.47, 33.16, 31.43, 29.88, 29.47, 28.70, 28.05, 27.15, 26.28, 25.50, 25.09, 22.58, 22.49, 13.20.



(**18e**): 62% Yield. ^1H NMR

(CD_3OD , 400 MHz): δ = 8.10 (d, J = 8.50 Hz, 2H), 7.98 (d, J = 8.30 Hz, 2H), 5.25 (d, J = 3.49 Hz, α -anomer), 4.77 (d, J = 8.34 Hz, β -anomer), 4.36 (t, J = 7.35 Hz, 1H), 3.92-3.71 (m, 4H), 3.46-3.34 (m, 4H), 3.25-3.15 (m, 2H), 2.68-2.44 (m, 7H), 2.10-1.98 (m, 2H), 1.92-1.81 (m, 7H), 1.63-1.52 (m, 4H), 1.39-1.24 (m, 11H), 0.91-0.88 (m, 6H). ^{13}C NMR (CD_3OD , 100 MHz): δ = 195.72, 174.67, 167.92, 138.80, 138.34, 128.58, 127.49, 91.40, 71.93, 71.45, 71.30, 62.42, 61.63, 54.65, 42.88, 42.63, 31.70, 31.45, 30.14, 28.73, 28.07, 27.16, 26.94, 25.10, 23.75, 22.45, 22.40, 17.56, 16.12, 13.23, 12.04.

Chapter Seven: Epilogue

A. Summary and conclusions.

The central focus in our research was to develop an efficient methodology leading to unique scaffolds with an emphasis on structural and functional diversity.

An experimentally straightforward, high-yielding photoinduced transformation of highly strained polycyclic oxetanes has been developed. The two step sequence, involving the *Diels-Alder* addition of heterocyclic chalcones to a variety of dienes, followed by the *Paternò-Büchi* photocycloaddition, was described in our group and referred to as an alkene-carbonyl oxametathesis [30 and Appendix E, reference C]. We further demonstrated that the *Diels-Alder* adducts of chromones are capable of photoinduced alkene-arene [2+2] cycloaddition producing dienes, which can either dimerize or be introduced into a double-tandem $[4_{\pi}+2_{\pi}]^{\circ}[2_{\pi}+2_{\pi}]^{\circ}[4_{\pi}+2_{\pi}]^{\circ}[2_{\pi}+2_{\pi}]$ synthetic sequence, followed by an acid-catalyzed oxametathesis [35 and Appendix E, reference B]. This methodology offers a rapid growth in molecular complexity over a few simple steps. Interestingly, conformationally unconstrained aliphatic compounds, resulting from the *Diels-Alder* addition of cyclohexadiene or cyclopentadiene to methyl vinyl ketone and followed by the *Paternò-Büchi* reaction, underwent an acid-catalysed oxametathesis as well. This observation proved the generality of the new approach.

In addition, we prepared polycyclic oxetanes resulting from the *Diels-Alder* adducts of cyclic ketones. This not only gave us access to remarkably strained oxetane systems, but also the mechanism for their protolytic ring fragmentation provided a great deal of insight to how the strain affects the reactivity [Appendix E, reference A].

We found that the *Sulfa-Diels-Alder* products did not produce *Paternò-Büchi* adducts upon irradiation. Nonetheless, both *exo*- and *endo*-3-benzoyl-2-thiabicyclo[2.2.1]hept-5-enes were photochemically active and assorted products with defined stereochemistry were produced during photolysis.

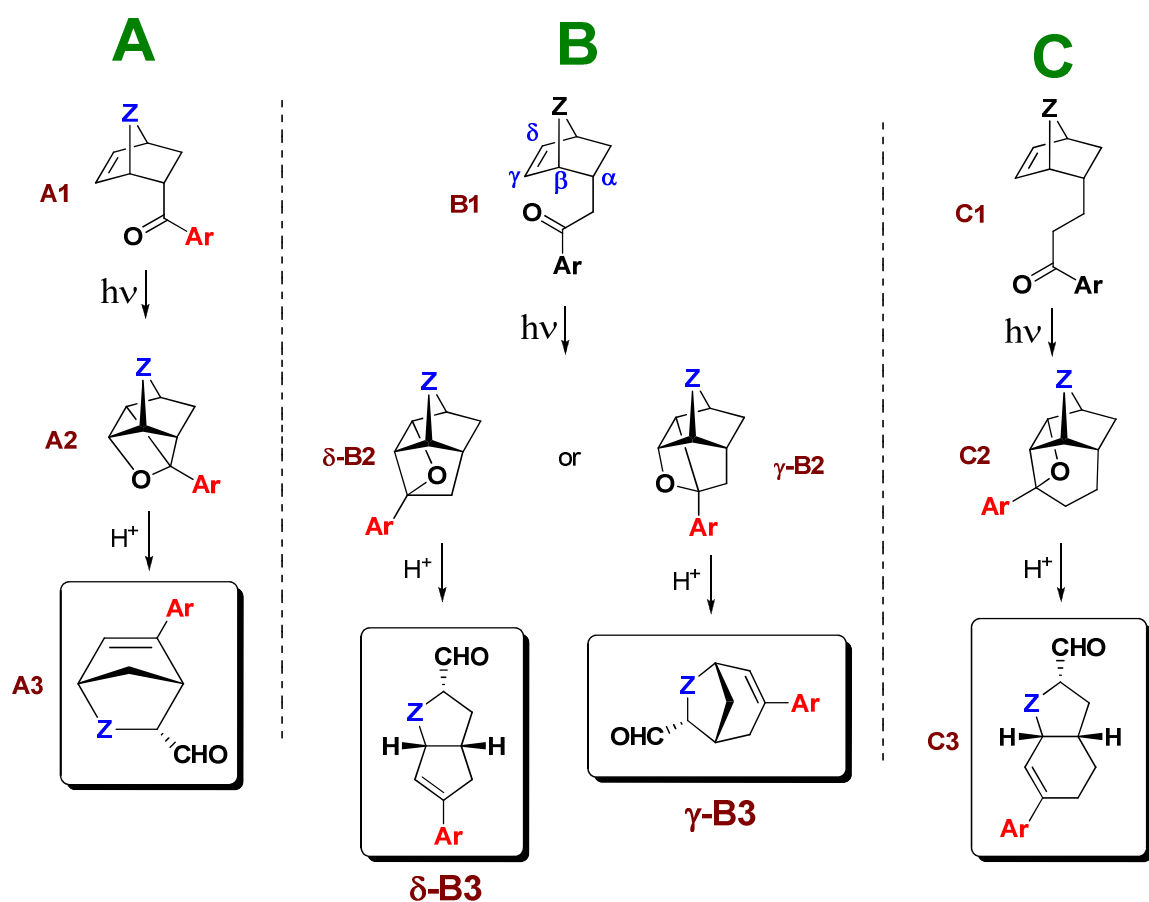
To demonstrate diverse utilization of light in combinatorial chemistry, we have developed an approach to the encoding and screening of solution phase libraries based on the photorelease of externally sensitized photolabile tags. The encoding tags can be released into solution only when a binding event occurs between the ligand and the receptor (biotin-avidin system), equipped with an electron transfer sensitizer. The released tags are analyzed in solution revealing the identity of the lead ligand [50 or Appendix E, reference J].

It should be mentioned that in our group we have developed other research projects which were not included in this dissertation (Appendix E, references D-I, K). The list of all publications, relevant to my work, can also be found in Appendix E.

B. Future development.

Since alkene-carbonyl oxametathesis discussed in this dissertation (Scheme 47A) showed such a tremendous potential for the diversity oriented synthesis, several projects related to this methodology are ongoing in our research group at this time.

We hypothesized that adducts containing *endo*-phenacyl group (type **B1**, Scheme 47B) would have been capable to produce δ -oxetanes. An extra methylene group between the bicyclic core and aromatic carbonyl (**B1**) might provide enough freedom for the oxygen atom to reach the farthest end of the double bond (δ -atom) during the *Paternò-Büchi* addition to form oxetane δ -**B2**. Subsequent protolytic oxametathesis would lead to the formation of potentially useful pentalene-like aldehydes δ -**B3** (Scheme 47B):

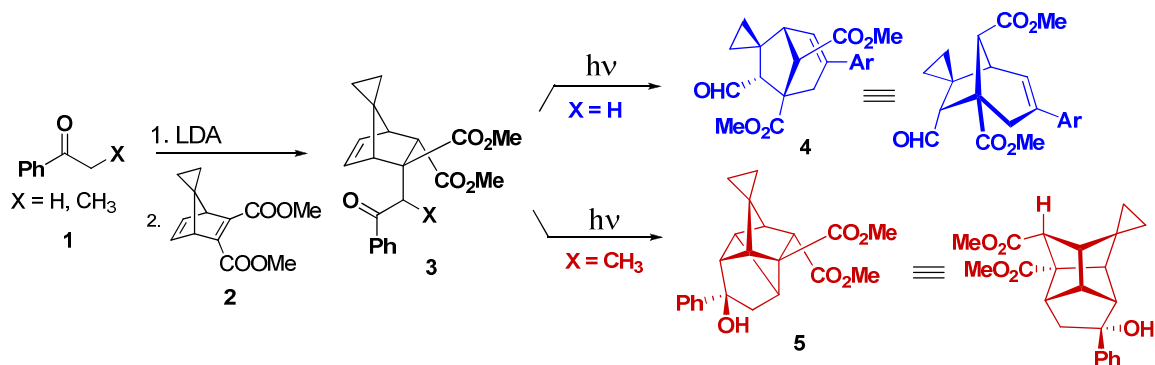


Scheme 47. (A) Oxametathesis in the aromatic and chromone-based series (γ -aldehydes); (B) Oxametathesis leading to the formation of δ - and γ -aldehydes; (C) Oxametathesis leading to the formation of δ -aldehydes.

However, we do not completely rule out the possibility of forming γ -oxetanes (γ -**B3**), similar to the observations described previously (Scheme 47A, Chapter Two, Three and Four). Only in this case the resulting aldehyde would contain a [3.n.1]-bicyclic core (as opposed to [2.n.1]).

It is logical to assume that two methylene groups separating the bicyclic core from the aroyl group (**C1**) would encourage the formation of solely δ -aldehydes (Scheme 47C).

This hypothesis is currently under extensive investigation in our group. Up to this point we have been able to obtain several adducts **3** (B1 in Scheme 47, **3** in Scheme 48) containing *endo*-benzoyl group. The synthesis is based on the *Michael* addition of enolate **1** to the *D*.-A. adduct **2** (Scheme 48):



Scheme 48. Preliminary results of photofragmentation of adducts **3**.

It is interesting that *Michael* adducts **3** (X = H) based on acetophenone underwent oxametathesis yielding γ -aldehyde **4** (Scheme 48). However, in the case of propiophenone adduct **3** (X = CH₃) did not produce an oxetane (even a trace amount) but rather rearranged forming alcohol **5** (Scheme 48). The mechanism for this transformation is under investigation.

References

1. An Introduction to medicinal chemistry. Graham L. Patrick. Oxford University Press, USA; 3 edition (June 23, **2005**).
2. <http://www.chem.pitt.edu/research/diversity-oriented-synthesis>
3. (a) Pittelkow, M.; Christensen, J. B. *Org. Lett.* **2005**, 7 (7), 1295 - 1298. (b) Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. *Angew. Chem. Int. Ed.* **2007**, 46, 4708 - 4711. (c) http://en.wikipedia.org/wiki/Convergent_synthesis
4. (a) The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century, Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, 39, 44 - 122. (b) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J. E.; Couladouros, A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, 367, 630 - 634. (c) Holton, R. A.; Somoza, C.; Kim, K. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, 116, 1597 - 1600. (d) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, 117, 1171 - 1172; Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, 117, 1173 - 1174. (e) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Reddy, K.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, 117, 10227 - 10238. (f) Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Winssinger, N.; Hughes, R.; Bando, T. *Angew. Chem.* **1998**, 111, 253 - 255; *Angew. Chem. Int. Ed.* **1999**, 38, 240 - 244.
5. Robinson, R. *J. Chem. Soc.* **1917**, 111, 762 - 768.
6. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, 115, 9421 - 9438.
7. (a) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, 128 (4), 1056 - 1057. (b) Heffron, T. P.; Simpson, G. L.; Merino, E.; Jamison, T. F. *J. Org. Chem.* **2010**, 75 (8), 2681 - 2701.
8. (a) Garanger, E.; Blois J.; Hilderbrand. S. A.; Shao, F.; Josephson, L. *J. Comb. Chem.*, **2010**, 12 (1), 57 - 64. (b) http://en.wikipedia.org/wiki/Divergent_synthesis
9. Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2006**, 45 (22), 3555 - 3715.
10. Multicomponent Reactions with Isocyanides, Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, 39, 3168 - 3210.

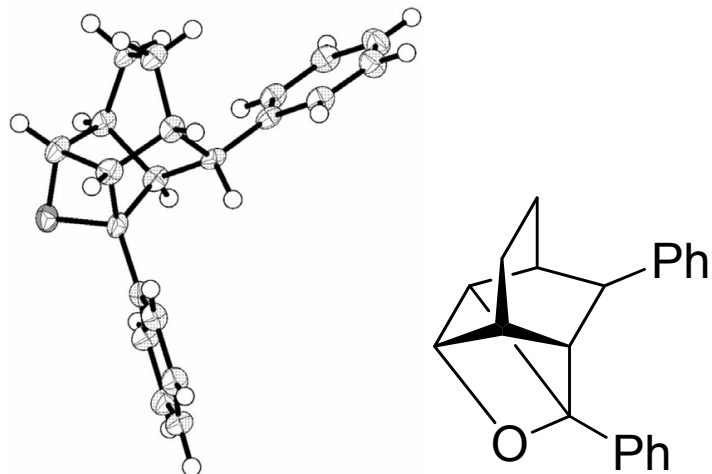
11. Ilyin, A.; Kysil V.; Krasavin M.; Kurashvili I.; Ivachtchenko A.V. *J. Org. Chem.* **2006**, *71*(25), 9544 - 9547.
12. Asinger, F. *Angew. Chem.* **1956**, *68*, 413.
13. Shaabani, A.; Maleki, A.; Mofakham, H.; Moghimi-Rad, J. *J. Org. Chem.* **2008**, *73*, 3925 - 3927.
14. Marcaccini, S.; Neo, G. A.; Marcos F. C. *J. Org. Chem.* **2009**, *74*, 6888 - 6890.
15. Paravidino, M.; Scheffelaar, R.; Schmitz, R. F.; Frans J. J. de Kanter, Groen, M. B.; Ruijter, E.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 10239 - 10242.
16. Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **1993**, *32*, 563 - 564.
17. Modern molecular photochemistry of organic molecules. Nicholas J. Turro, V. Ramamurthy, J. C. Scaiano. University Science Books, California; **(2010)**.
18. Liu, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89* (19), 4936 - 4944.
19. Kohmoto, S.; Noguchi, T.; Masu, H.; Kishikawa, K.; Yamamoto, M.; Yamaguchi, K. *Org. Lett.* **2004**, *6* (5), 683 - 685.
20. Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052 - 1103.
21. Hoffmann, U.; Gao, Y.; Pandey, B.; Klinge, S.; Warzecha, K. D.; Krueger, C.; Roth, H. D.; Demuth, M. *J. Am. Chem. Soc.*, **1993**, *115* (22), 10358 - 10359.
22. Yen, C.-F.; Liao, C.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4090 - 4093.
23. Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Tomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8453 - 8463.
24. Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131 - 5135.
25. Dynamic Combinatorial Chemistry, Corbett, P. T.; Leclaire J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652 - 3711.
26. Lam, R. T. S.; Belenguer, A.; Roberts, S. L.; Naumann, C.; Jarrosson, T.; Otto, S.; Sanders, J. K. M. *Science* **2005**, *308*, 667 - 669.
27. Rawal, V. H.; Dufour, C. *J. Am. Chem. Soc.* **1994**, *116*, 2613 - 2614.
28. (a) Jones, G.; Schwartz, S. B.; Marton, M. T. *Chem. Commun.* **1973**, *11*, 374 - 375. (b) Jones, G.; Acquadro, M. A.; Carmody, M. A. *Chem. Commun.* **1975**, *6*, 206 - 207.

29. Perez-Ruiz, R.; Miranda, M. A.; Alle, R.; Meerholz, K.; Griesbeck, A. *Photochem. Photobiol. Sci.* **2006**, 5, 51 - 55.
30. Valiulin, R. A.; Kutateladze, A. G. *Org. Lett.* **2009**, 11 (17), 3886 - 3889.
31. Syntheses of heterocyclic chalcones are extensively documented: (a) Özdemir, A.; Turan-Zitouni, G.; Kaplancikli, Z. A.; Revial, G.; Güven, K. *Eur. J. Med. Chem.* **2007**, 42, 403 - 409. (b) Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeonh, B.-S.; Jeong, T. C.; Lee, C.-S.; Lee, E.-S. *Bioorg. Med. Chem.* **2007**, 15, 4351 - 4359. (c) Ziener, U.; Lehn, J.-M.; Mourran, A.; Möller, M. *Chem.-Eur. J.* **2002**, 8, 951 - 957. (d) Butkiewicz, K. *Electroanal. Chem. Interfacial Electrochem.* **1972**, 39, 419 - 428. (e) Marvel, C. S.; Coleman, L. E., Jr.; Scott, G. P. *J. Org. Chem.* **1955**, 20, 1785 - 1792. (f) Durinda, J.; Szücs, L.; Krasnec, L.; Heger, J.; Springer, V.; Kolena, J.; Keleti, J. *Acta Fac. Pharm. Bohemoslov.* **1966**, 89 - 129.
32. (a) Filipescu, N.; Menter, J.M. *J. Chem. Soc. B* **1969**, 616 - 620. (b) Kushner, A. S. *Tetrahedron Lett.* **1971**, 35, 3275 - 3278.
33. (a) Marchand, A. P.; Zope, U. R.; Burritt, A.; Bott, S. G.; Coxon, J. M. *Tetrahedron* **1995**, 51, 9319 - 9326. (b) Coxon, J. M.; Fong, S. T.; Lundie, K.; McDonald, D. Q.; Steel, P. J.; Marchand, A. P.; Zaragoza, F.; Zope, U. R.; Rajagopal, D.; et al. *Tetrahedron* **1994**, 50, 13037 - 13048. (c) Coxon, J. M.; MacLagan, R. G. A. R.; McDonald, D. Q.; Steel, P. J. *J. Org. Chem.* **1991**, 56, 2542 - 2549. (d) Coxon, J. M.; O'Connell, M. J.; Steel, P. J. *J. Org. Chem.* **1987**, 52, 4726 - 4732.
34. Hsung R. P. *J. Org. Chem.* **1997**, 62, 7904 - 7905.
35. Valiulin, R. A.; Kutateladze, A. G. *Tetrahedron Lett.* **2010**, 51, 3803 - 3806.
36. (a) Sauers, R. R.; Kelly, K. W.; Sickles, B. R. *J. Org. Chem.* **1972**, 37, 537 - 543. (b) Saures, R. R.; Henderson, T. R. *J. Org. Chem.* **1974**, 39 (13), 1850 - 1853.
37. Gasteiger, J.; Dammer, O. *Tetrahedron* **1978**, 34, 2939 - 2945.
38. Valiulin, R. A.; Dressen, D. G.; Riggs, J. R.; Habte, F. M.; Kutateladze, A. G. *J. Org. Chem.* **2009**, 74, 3484 - 3490.
39. Hill, R. K.; Newton, M. G.; Pantaleo, N. S.; Collins, K. M. *J. Org. Chem.* **1980**, 45, 1593 - 1596.
40. (a) Paulvannan, K.; Jacobs, J. W. *Tetrahedron* **1999**, 55, 7433 - 7440. (b) Murali, R.; Rao, H. S. P.; Scheeren, H. W. *Tetrahedron* **2001**, 57, 3165 - 3174. (c) Benningshof, J. C. J.; Blaauw, R. H.; van Ginkel, A. E.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Chem. Soc., Perkin Trans.* **2002**, 1, 1693 -

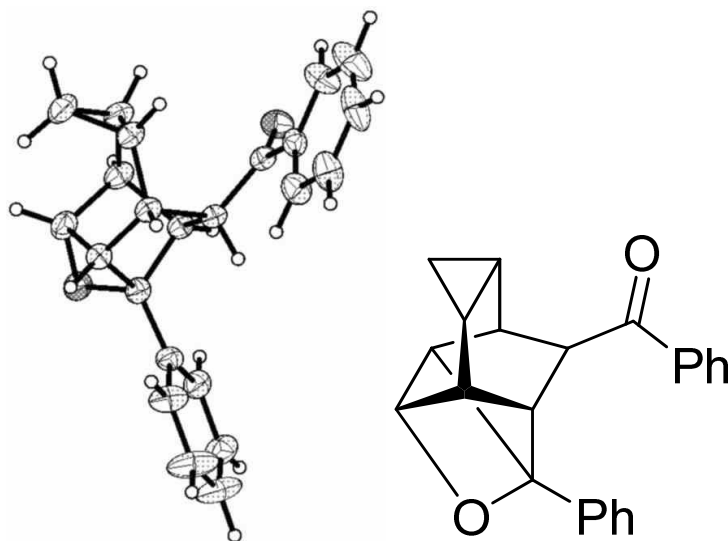
1700. (d) Kachkovskiy G. O.; Kolodiazhnyi, O. I. *Tetrahedron* **2007**, *63*, 12576 - 12582. (e) Ikoma, M.; Oikawa, M.; Sasaki, M. *Tetrahedron* **2008**, *64*, 2740 - 2749.
41. (a) Margetic, D.; Warrenner, R. N.; Sun, G.; Butler, D. N. *Tetrahedron* **2007**, *63* (20), 4338 - 4346. (b) Warrenner, R. N.; Margetic, D.; Sun, G.; Russell, R. A. *Australian J. Chem.* **2003**, *56* (4), 263 - 267. (c) Paulvannan, K. *J. Org. Chem.* **2004**, *69*, 1207 - 1214.
42. Papa, D.; Schwenk, E.; Villani, F.; Klingsberg, E. *J. Am. Chem. Soc.* **1948**, *70*, 3356 - 3360.
43. Bianchi, M.; Butti, A.; Christidis, Y.; Perronnet, J.; Barzaghi, F.; Cesana, R.; Nencioni, A. *Eur. J. Med. Chem.* **1988**, *23*, 45 - 52.
44. Kirby, G. W.; Lothead, A. W.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1984**, *14*, 922 - 923.
45. Block, E.; Wall, A. *J. Org. Chem.* **1987**, *52*, 809 - 818.
46. Corrie, J. E. T.; Kirby, G. W.; Mackinnon, J. W. M. *J. Chem. Soc. Perkin Trans. I* **1985**, *4*, 883 - 886.
47. Lam, K. S.; Lebl, M.; Krchňák, V. *Chem. Rev.* **1997**, *97*, 411 - 448.
48. Baldino, C. M. *J. Combinatorial Chem.* **2000**, *2*, 89 - 103.
49. Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J.; Freier, S. M. *J. Med. Chem.* **1997**, *40*, 4386 - 4395.
50. Kottani, R.; Valiulin, R. A.; Kutateladze, A. G. *PNAS* **2006**, *103* (38), 13917 - 13921.
51. (a) Mitkin, O. D.; Kurchan, A. N.; Wan, Y.; Schiwal, B. F.; Kutateladze, A. G.; *Org. Lett.* **2001**, *3*, 1841 - 1844. (b) Mitkin, O. D.; Wan, Y.; Kurchan, A. N.; Kutateladze, A. G. *Synthesis* **2001**, *7*, 1133 - 1142. (c) Wan, Y.; Angleson, J. K.; Kutateladze, A. G. *J. Am. Chem. Soc.* **2002**, *124*, 5610 - 5611.
52. Gustafson, T. P.; Kurchan, A. N.; Kutateladze, A. G. *Tetrahedron* **2006**, *62*, 6574 - 6580.
53. Valiulin, R. A.; Kottani, R.; Kutateladze, A. G. *J. Org. Chem.* **2006**, *71*, 5047 - 5049.
54. (a) Paquette, L. A.; Carr, R. V. C. *J. Am. Chem. Soc.* **1980**, *102*, 7553 - 7559. (b) Sawaki, Y.; Foote, C. S. *J. Org. Chem.* **1983**, *48*, 4934 - 4940.

Appendix A

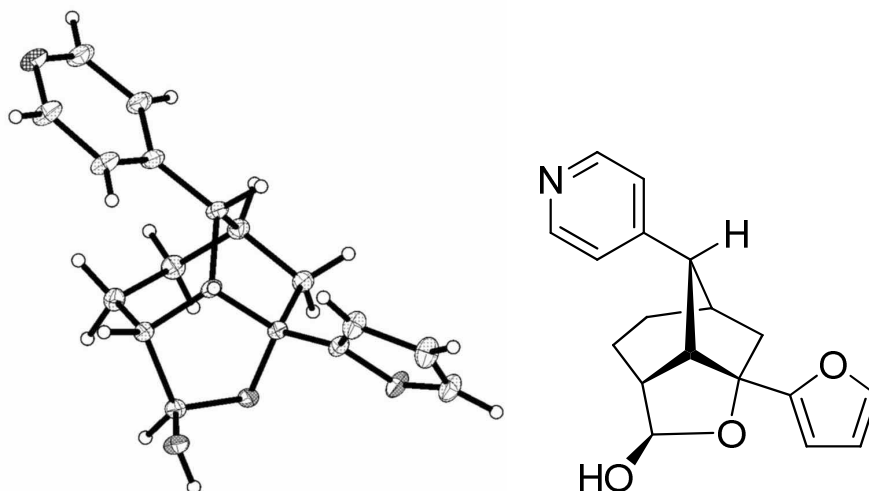
4,7-Diphenyl-3-oxatetracyclo[4.2.2.0^{2,5}.0^{4,8}]decane (2e): This crystal structure has been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 727386.



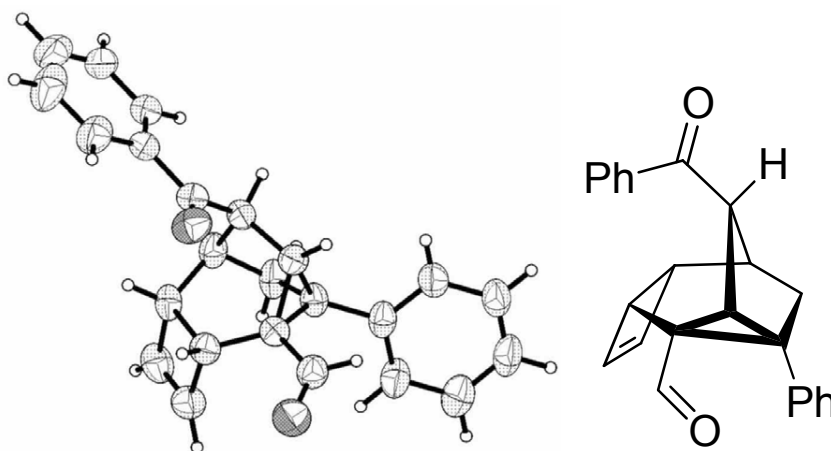
11-Benzoyl-4-phenyl-3-oxapentacyclo[4.3.2.0^{2,5}.0^{4,10}.0^{7,9}]undecane (2r): This crystal structure has been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 727711.



1-(2-Furanyl)-8-(4-pyridyl)-2-oxatricyclo[4.2.1.0^{4,9}]decan-3-ol (4h): This crystal structure has been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 727710.

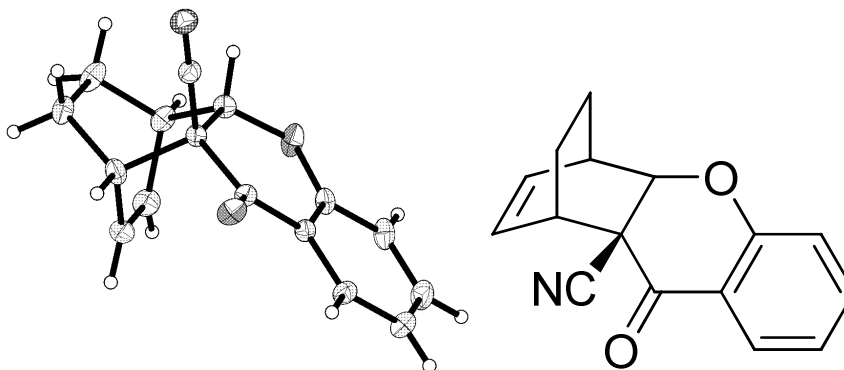


***syn*-10-Benzoyl-9-phenyltertracyclo[5.2.1.0.2,9^{03,6}]dec-4-ene-2-carboxaldehyde (5t):** This crystal structure has been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 727709.

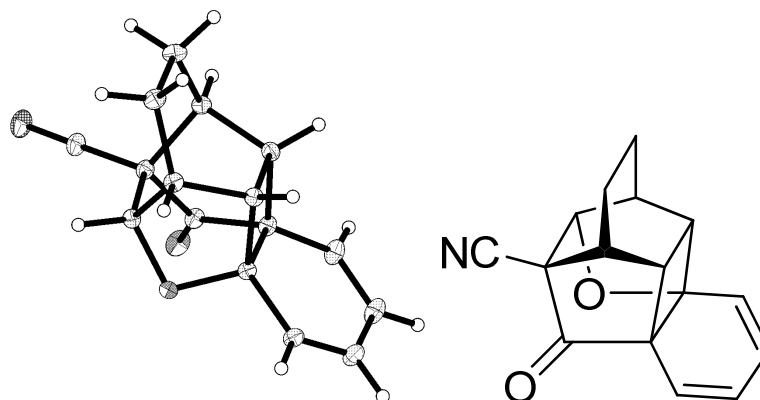


Appendix B

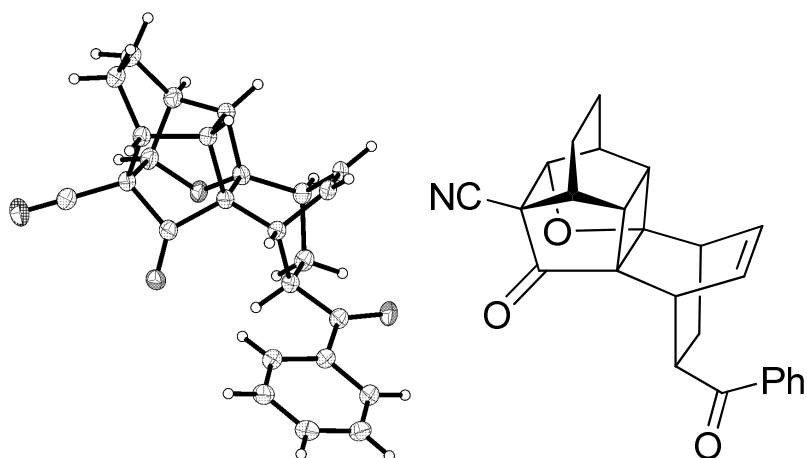
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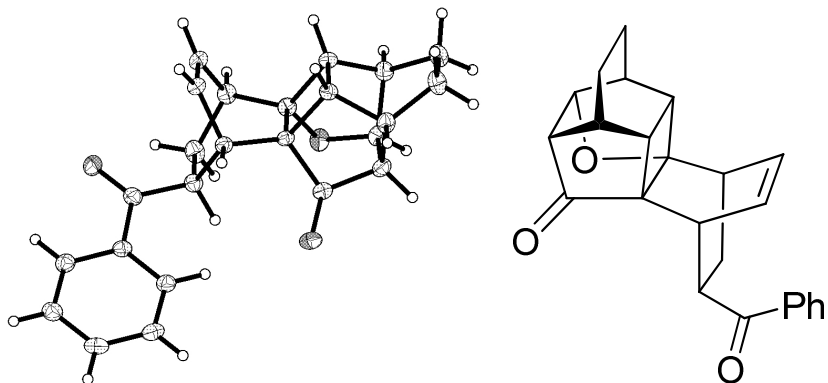
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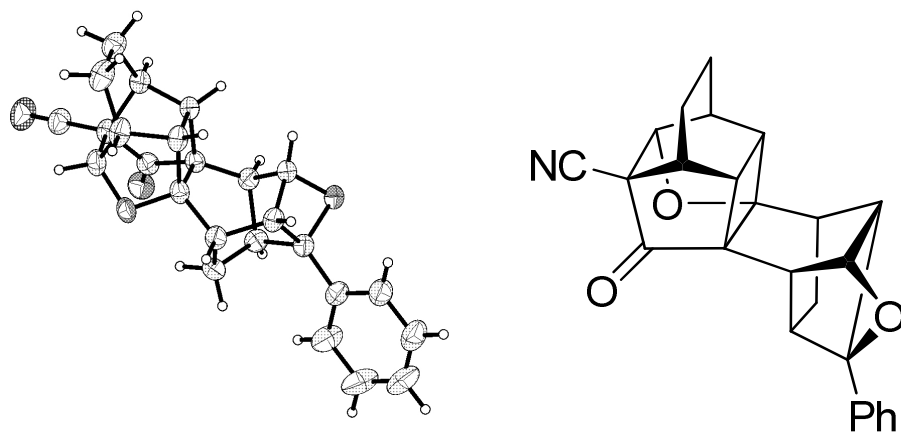
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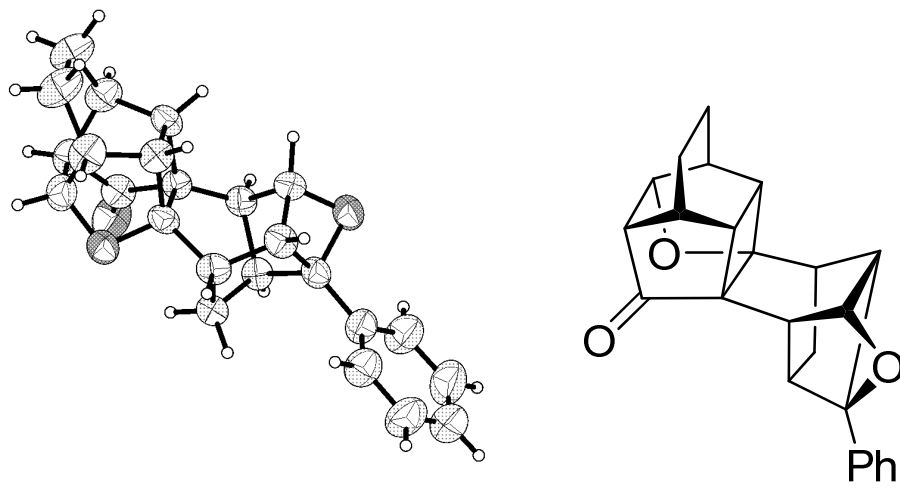
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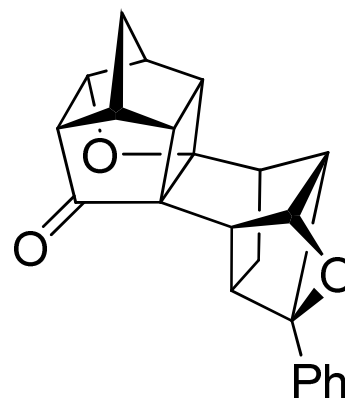
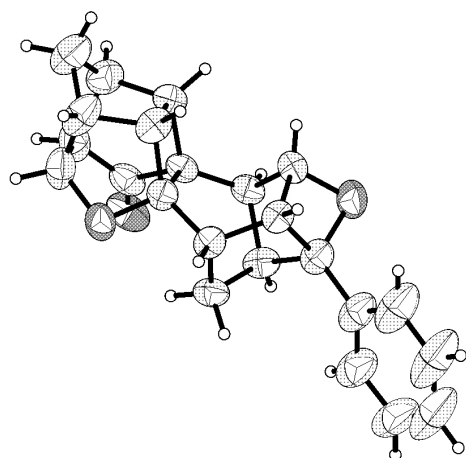
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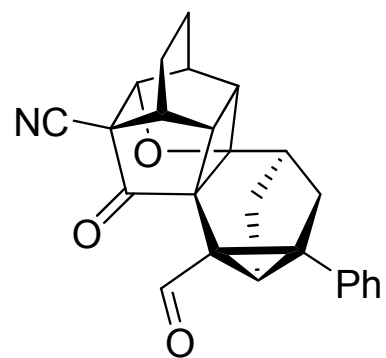
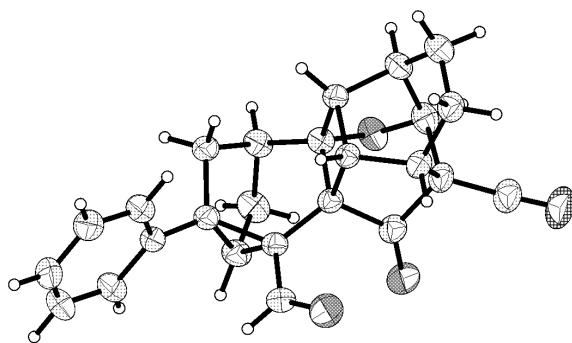
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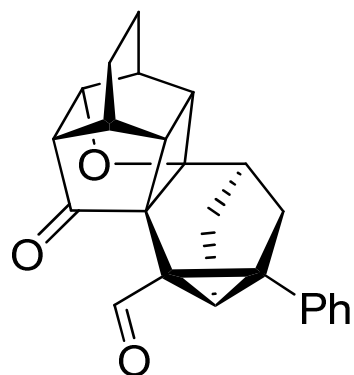
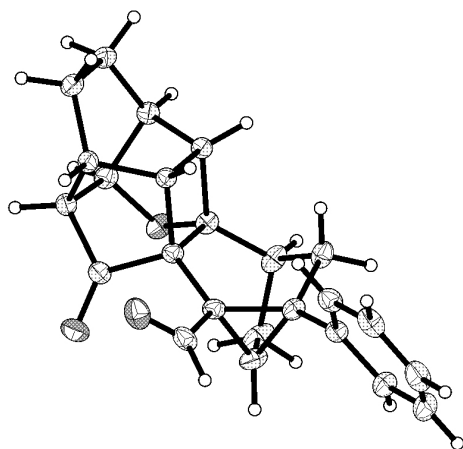
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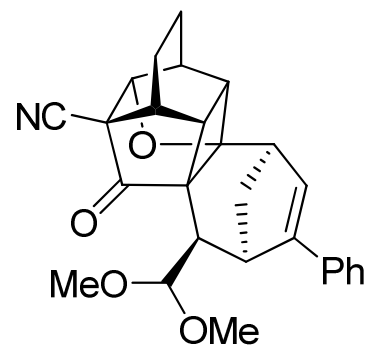
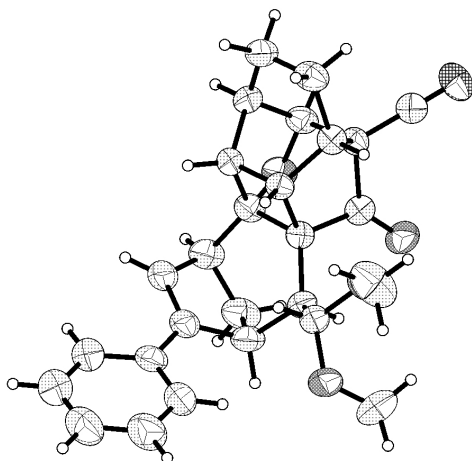
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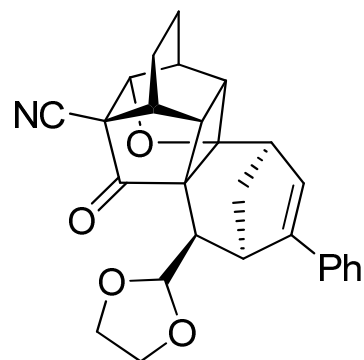
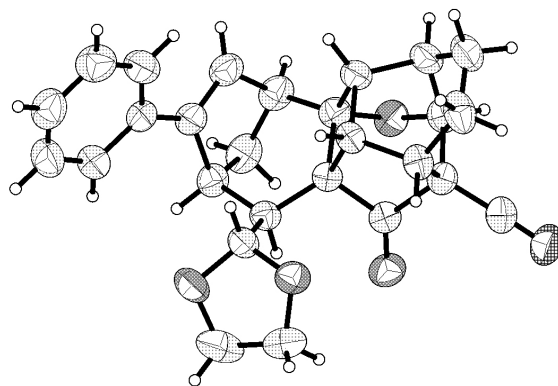
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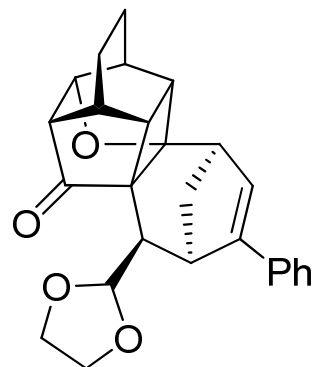
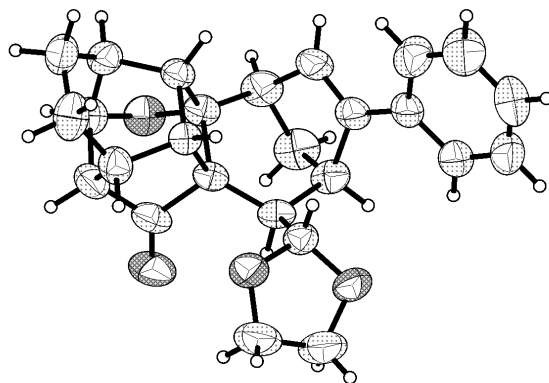
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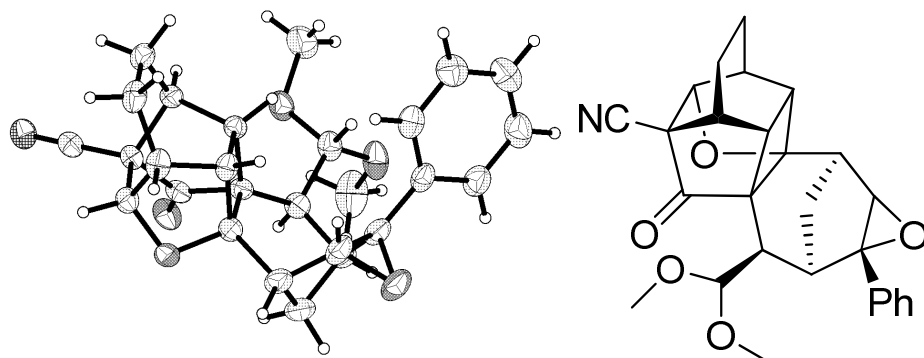
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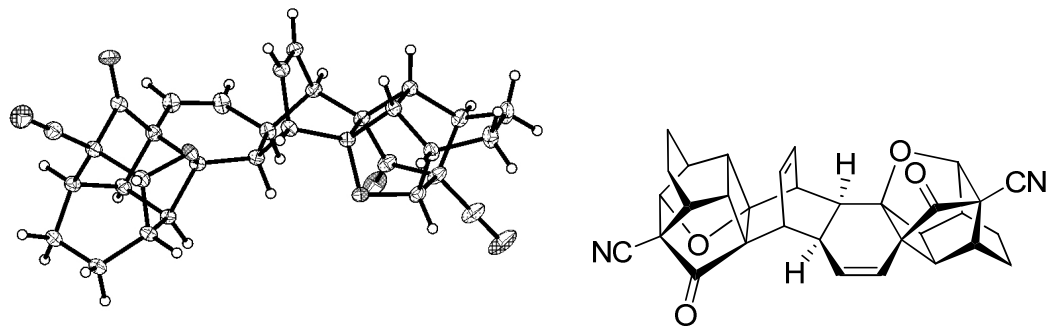
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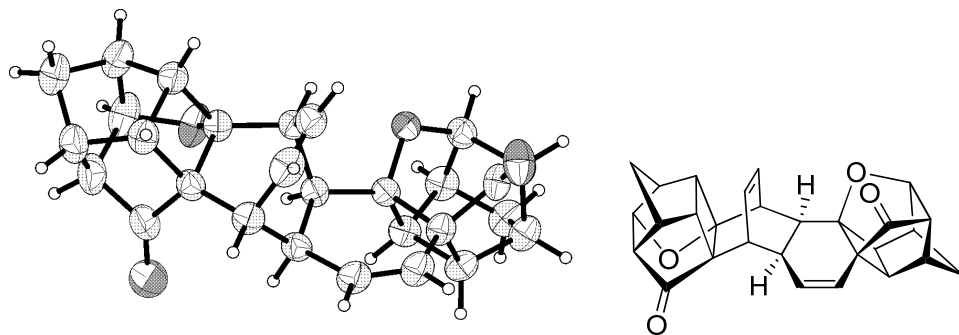
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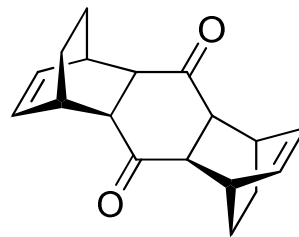
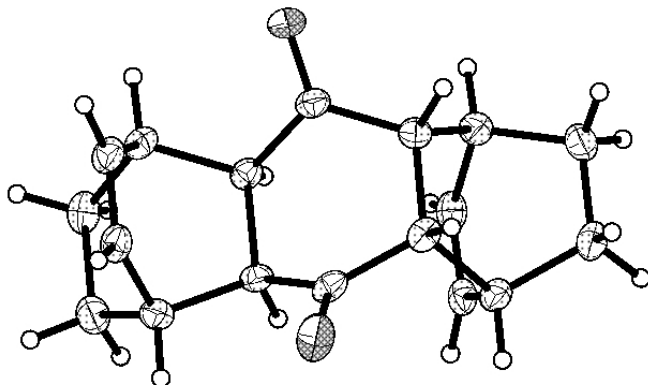


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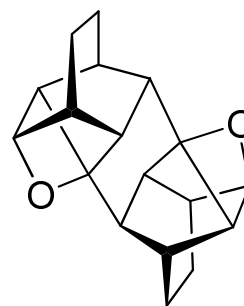
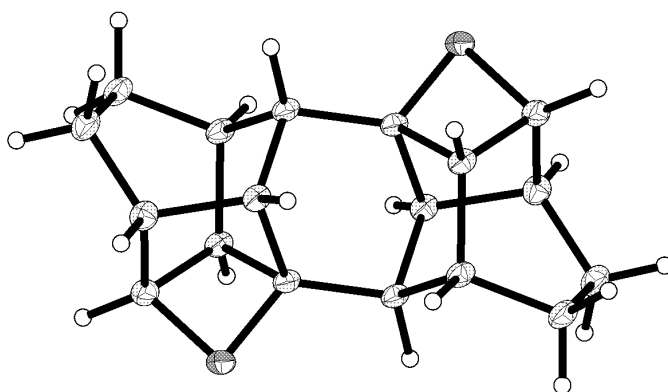


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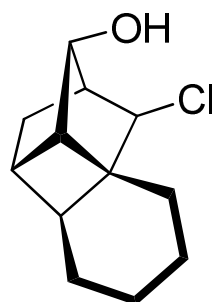
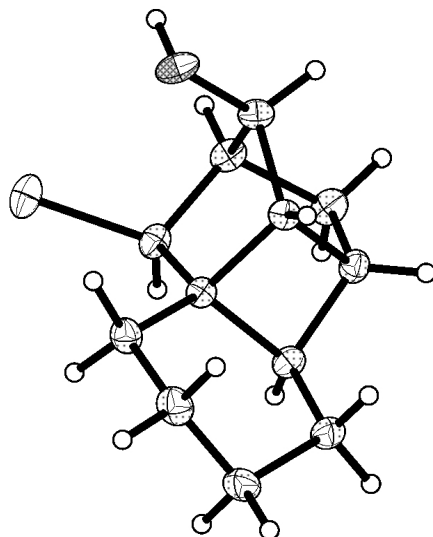
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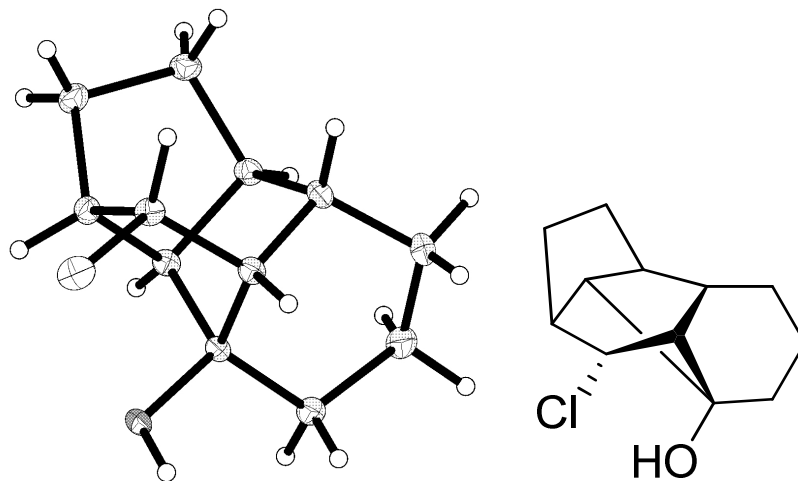
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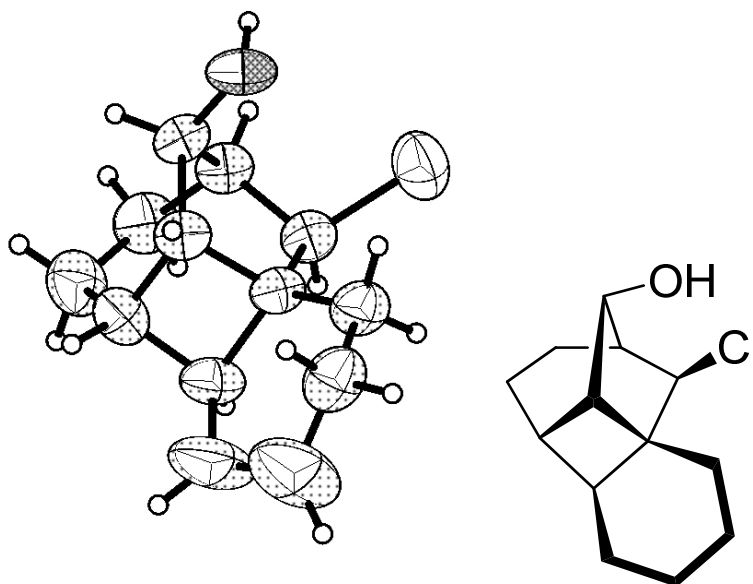
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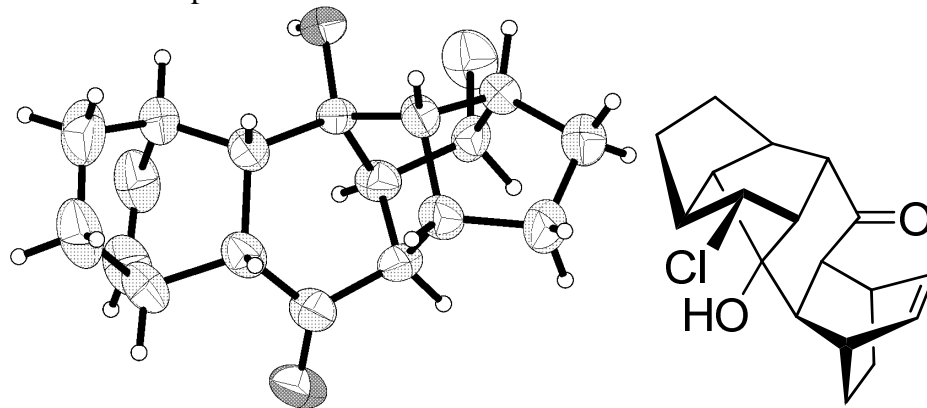
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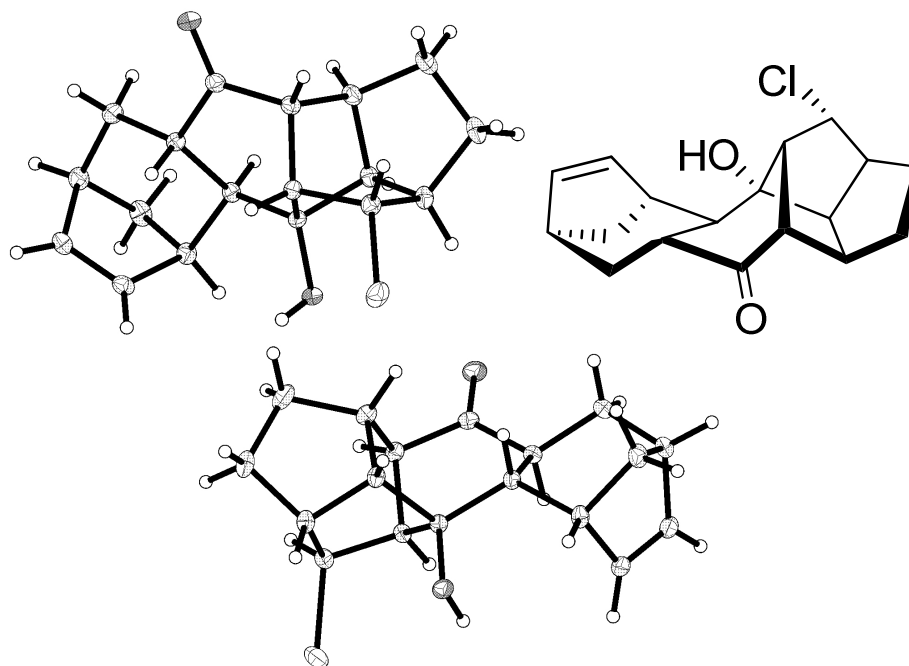
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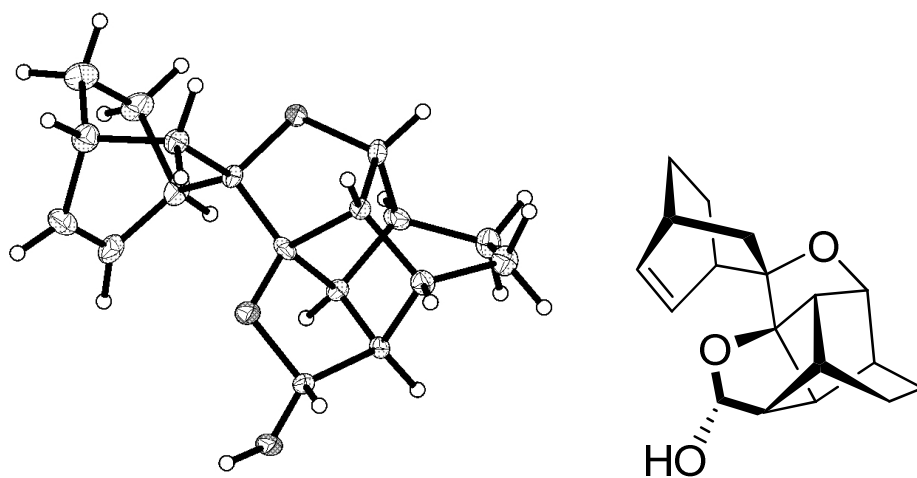
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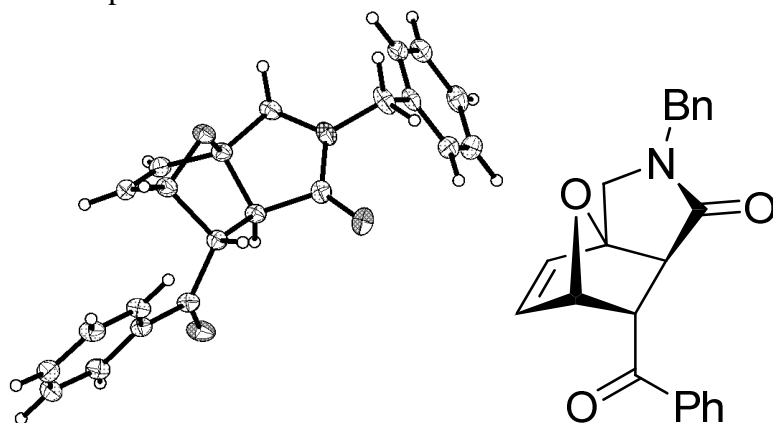
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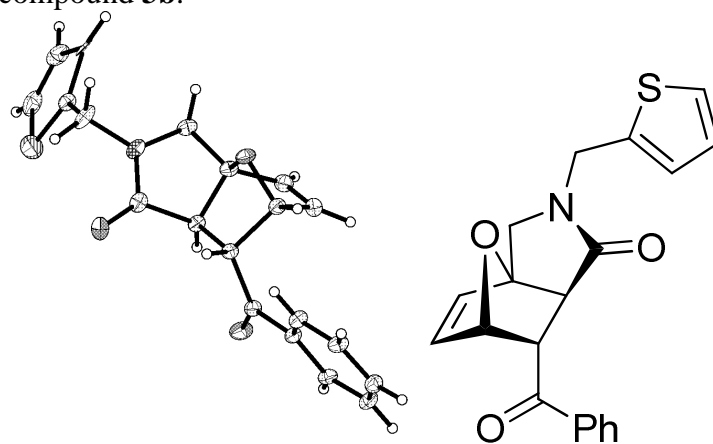
Appendix D

Part I:

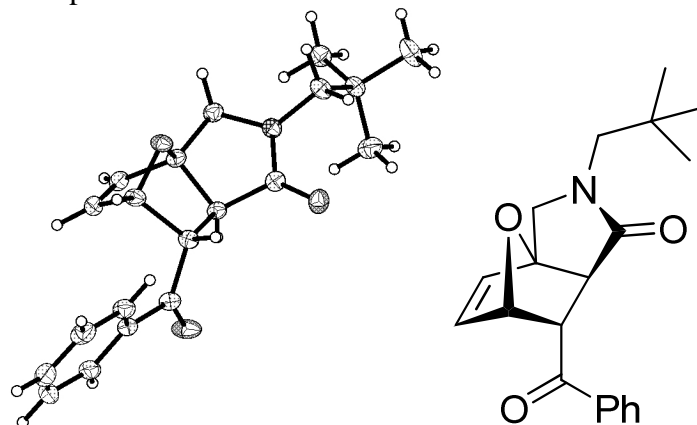
3a-1.cif cif file of compound **3a-1**:



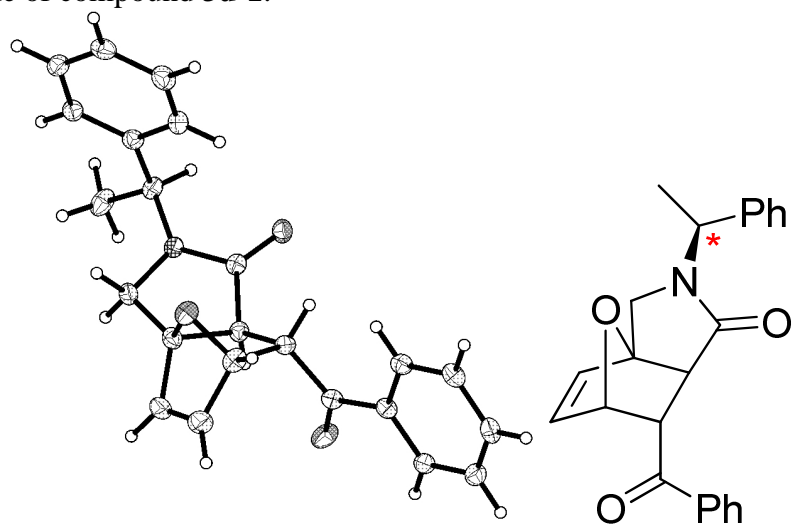
3b.cif cif file of compound **3b**:



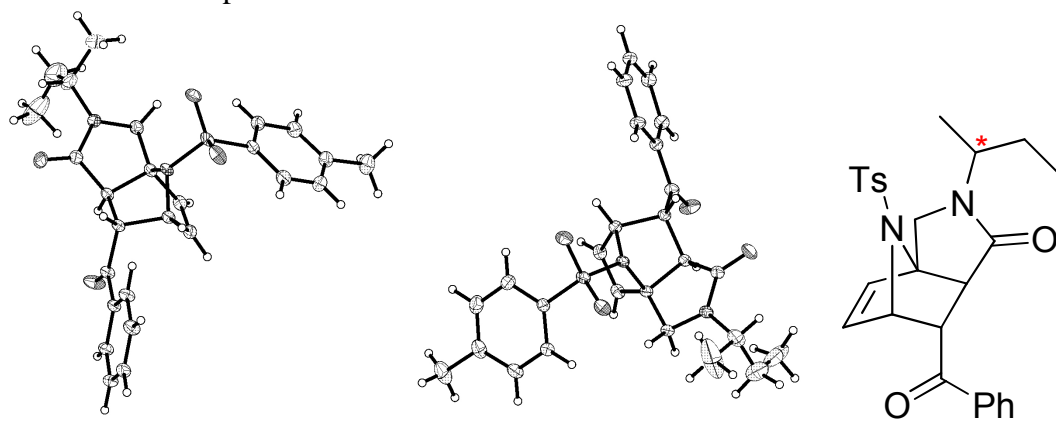
3c-1.cif cif file of compound **3c-1**:



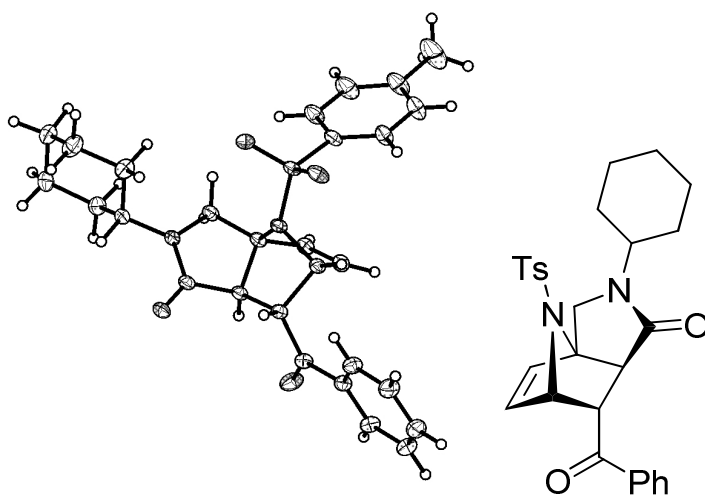
3d-1.cif cif file of compound **3d-1**:



3h.cif cif file of compound **3h**:

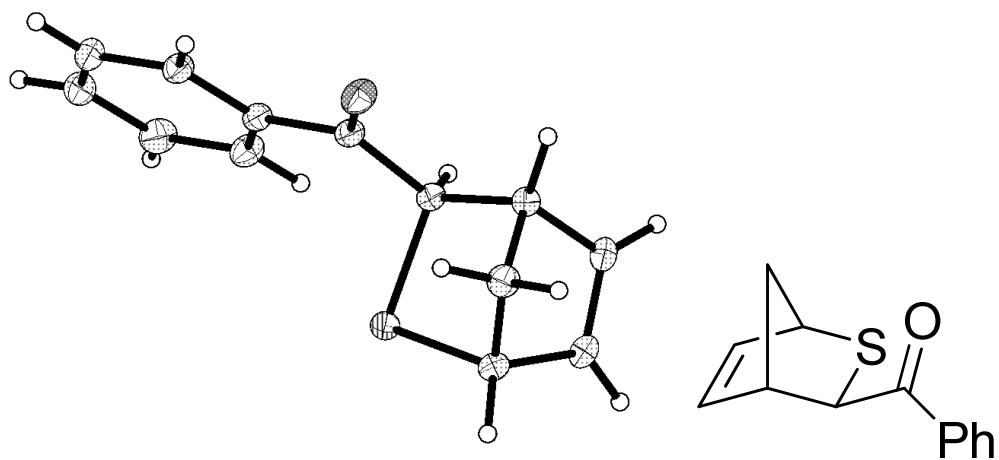


3i.cif cif file of compound **3i**:

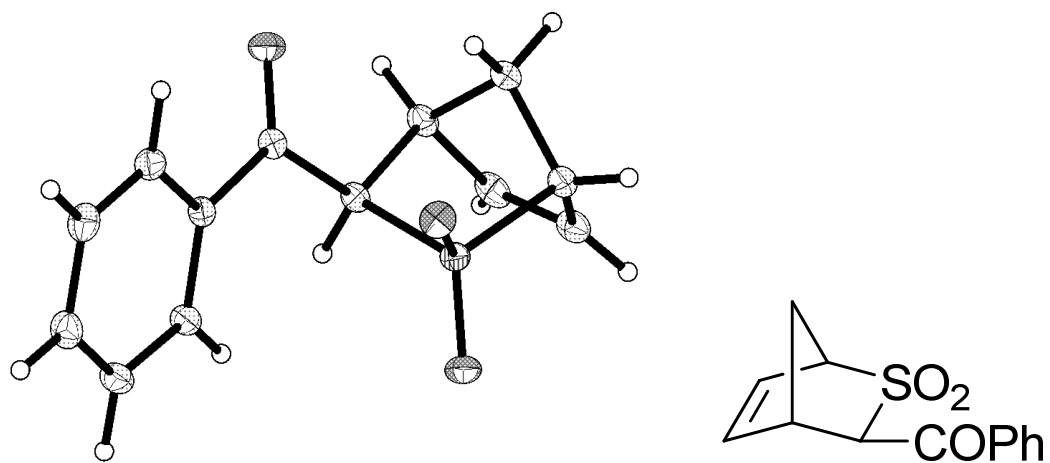


Part II:

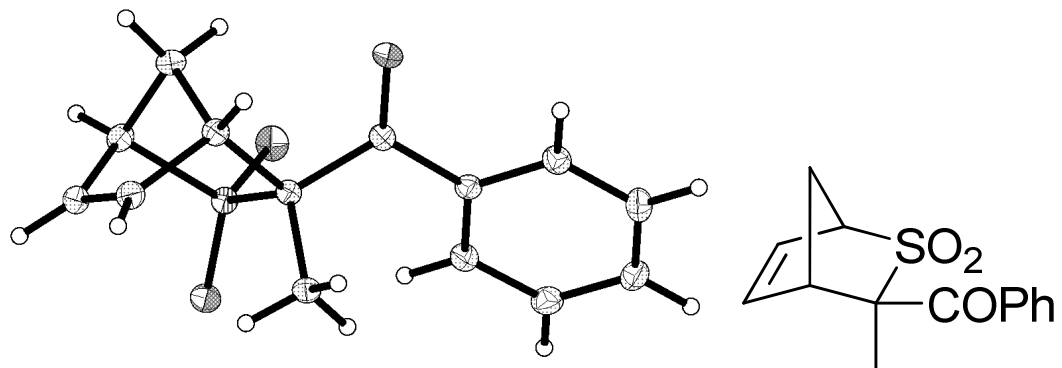
exo-2a.cif cif file of compound ***exo-2a***:



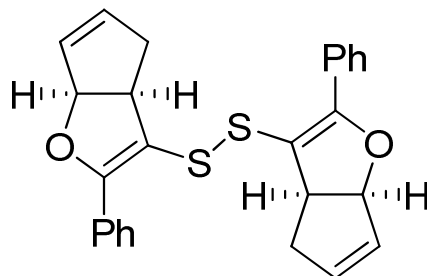
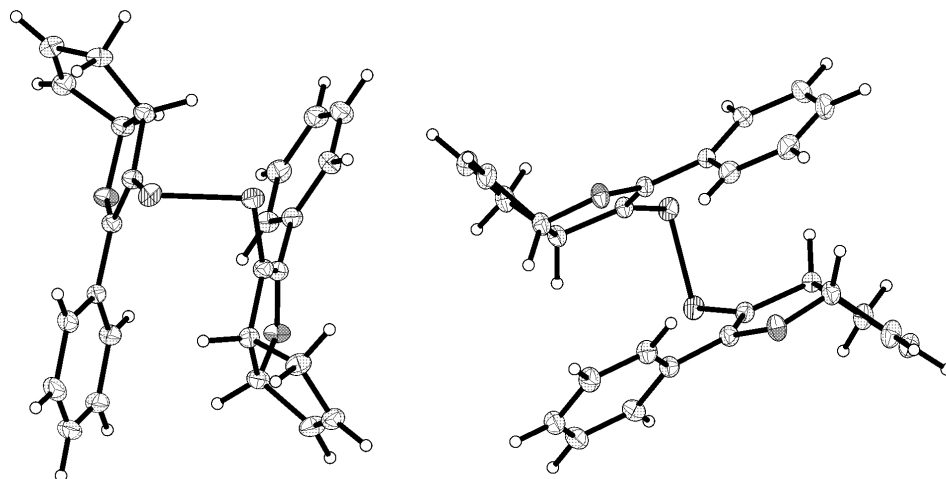
exo-3a.cif cif file of compound ***exo-3a***:



exo-3b.cif cif file of compound ***exo-3b***:



5a-2.cif cif file of compound **5a-2**:



Appendix E

(Papers published at the University of Denver, 2006-2010)

- A. *Strained to the Limit: When a Cyclobutyl Moiety Becomes a Thermodynamic Sink in a Protolytic Ring Opening of Photogenerated Oxetanes.* Valiulin, R. A.; Arisco, T. M.; Kutateladze, A. G. *Org. Lett.* **2010**, *in press*.
- B. *First Example of Intramolecular $[2\pi+2\pi]$ Alkene-Arene Photocyclization in the Chromone Series and its Synthetic Utility.* Valiulin, R. A.; Kutateladze, A. G. *Tetrahedron Lett.* **2010**, *51*, (29), 3803 - 3806.
- C. *Harvesting the Strain Installed by a Paternò-Büchi Step in a Synthetically Useful Way: High Yielding Photo-Protolytic Oxametathesis in Polycyclic Systems.* Valiulin, R. A.; Kutateladze, A. G. *Org. Lett.* **2009**, *11*, (17), 3886 - 3889.
- D. *Effect of Intramolecular Paternò-Büchi Reaction on the Thermodynamics and Kinetics of Nearly Degenerate $[3,3]$ -Sigmatropic Shift in Fluxional Polycycles.* Valiulin, R. A.; Dressen, D. G.; Riggs, J. R.; Habte, F. M.; Kutateladze, A. G. *J. Org. Chem.* **2009**, *74*, (9), 3484 - 3490.
- E. *A Peculiar Quenching Concentration Dependence of Photoinduced Fragmentation in Dithiane-Carbonyl Adducts: A Mechanistic Experimental and Theoretical Study.* Valiulin, R. A.; Lakkakula, S.; Kutateladze, A. G. *J. Photochem. Photobiol. A Chemistry* **2009**, *206*, 80 - 86.
- F. *Effect of beta-Alkylthioethyl Substitution in 1,3-Dithianes: Quasi-Anchimeric Assistance in Photoinduced Electron Transfer?* Valiulin, R. A.; Kutateladze, A. G. *J. Org. Chem.* **2008**, *73*, (16), 6393 - 6396.
- G. *2,6,7-Trithiabicyclo[2.2.2]octanes as Promising Photolabile Tags for Combinatorial Encoding.* Valiulin, R. A.; Kutateladze, A. G. *J. Org. Chem.* **2008**, *73*, (1), 335 - 338.
- H. *Interrupted Oligomerization Revisited: Simple and Efficient One Pot Multicomponent Approach to Versatile Synthetic Intermediates.* Valiulin, R. A.; Halliburton, L. M.; Kutateladze, A. G. *Org. Lett.* **2007**, *9*, (20), 4061 - 4063.
- I. *Photoactive Barbiturate Receptors: An Ultimate Lock-and-Key System in Which the Key Unlocks the Lock.* Lakkakula, S.; Mitkin, O. D.; Valiulin, R. A.; Kutateladze, A. G. *Org. Lett.* **2007**, *9*, (6), 1077 - 1079.

- J. *Direct Screening of Solution Phase Combinatorial Libraries Encoded with Externally Sensitized Photolabile Tags*. Kottani, R.; Valiulin, R. A.; Kutateladze, A. G. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, (38), 13917 - 13921.
- K. *Conformational Analysis of Spiro-Bis-Dithiepins: a Peculiar Case of Axial Chirality*. Wade, E. O.; Valiulin, R. A.; Ruybal, L. A.; Kutateladze, A. G. *Org. Lett.* **2006**, *8*, (22), 5121 - 5124.
- L. *When Ethyl is Infinitely Different from Methyl: Double Addition of Lithiated Dithianes to Aromatic Carboxylates Revisited*. Valiulin, R. A.; Kottani, R.; Kutateladze, A. G. *J. Org. Chem.* **2006**, *71*, (13), 5047 - 5049.